

EXHIBIT A

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, : MDL NO. 2875
LOSARTAN, AND :
IRBESARTAN PRODUCTS : HON. ROBERT
LIABILITY LITIGATION : B. KUGLER

THIS DOCUMENT APPLIES :
TO ALL CASES :

- CONFIDENTIAL INFORMATION -
SUBJECT TO PROTECTIVE ORDER

September 16, 2021

Videotaped remote deposition of MICHAEL B. BOTTORFF, Pharm.D., taken pursuant to notice, was held via Zoom Videoconference, beginning at 9:04 a.m., EST, on the above date, before Michelle L. Gray, a Registered Professional Reporter, Certified Shorthand Reporter, Certified Realtime Reporter, and Notary Public.

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Testimony of:

MICHAEL B. BOTTORFF, Pharm.D.

By Mr. Vaughn 11, 370
By Ms. Thompson 356

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2

THE VIDEOGRAPHER: We are

3

now on the record. My name is

4

Judy Diaz. I'm a legal

5

videographer for Golkow Litigation

6

Services.

7

Today's date is

8

September 16, 2021, and the time

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is 9:04 a.m.

10

This remote video deposition

11

is being held in the matter of

12

Valsartan, Losartan, and

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Irbesartan Products Liability

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Litigation MDL for the United

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States District Court District of

16

New Jersey.

17

The deponent is Dr. Michael

18

Bottorff.

19

All parties to this

20

deposition are appearing remotely

21

and have agreed to the witness

22

being sworn in remotely.

23

All counsel will be noted on

24

the stenographic record.

1 The court reporter is
2 Michelle Gray and will now swear
3 in the witness.

4 - - -

5 ... MICHAEL B. BOTTORFF, Pharm.D.,
6 having been first duly sworn, was
7 examined and testified as follows:

8 - - -

9 EXAMINATION

10 - - -

11 BY MR. VAUGHN:

12 Q. Doctor, can you introduce
13 yourself for the jury?

14 A. Yes. Michael Bottorff.

15 Q. And am I saying it right,
16 Bottorff?

17 A. That's good.

18 Q. All right. I'll try my best
19 not to butcher that.

20 A. No problem.

21 Q. Have you ever had your
22 deposition taken before?

23 A. I'm sorry. The question?

24 Q. Have you previously had your

1 deposition taken in any matter?

2 A. Yes, I have.

3 Q. Was that a yes?

4 A. Yes.

5 Q. And what litigations were
6 those?

7 A. There was an amiodarone
8 litigation that I think we've disclosed.
9 That's the only one that's been in the
10 last maybe four or five years. Prior to
11 that I did some depositions in Niaspan
12 patent law. And then a couple of
13 personal injury depositions probably back
14 in the 1990s.

15 Q. Okay. There's only -- was
16 the first one a drug case that you were
17 an expert in?

18 A. In the '90s, yes.

19 Q. And were you on the
20 plaintiffs' or the defense side?

21 A. Defense.

22 Q. And have you ever had your
23 deposition taken via Zoom before?

24 A. No.

1 Q. If you have any problems
2 hearing me just let me know. Okay?

3 A. I will.

4 Q. All right. And then for the
5 court reporter's sake, let's try our best
6 not to talk over each other and give, you
7 know, the defense attorney time to make
8 her objections, if she has any. Is that
9 fair?

10 A. Yes.

11 Q. And do you understand that
12 if there are objections, those are just
13 between the defense attorney and myself
14 and they shouldn't influence your answers
15 in any way?

16 A. I understand.

17 Q. And you're an expert for the
18 defense in this litigation, correct?

19 A. Correct.

20 Q. And as an expert, you're
21 aware that I'm allowed to ask you
22 hypothetical questions, right?

23 A. Yes.

24 Q. And if you don't understand

1 my questions, you'll let me know, right?

2 A. I will.

3 Q. Okay. So I want to explore
4 just some of your opinions first and the
5 basis for those opinions. And so, kind
6 of reading through here, I guess my first
7 question is, Dr. Bottorff, is it your
8 opinion that generic valsartan
9 contaminated with NDMA or NDEA has the
10 same monetary value as generic valsartan
11 without NDMA or NDEA?

12 MS. THOMPSON: Objection.
13 Form. Compound.

14 THE WITNESS: So the
15 question, as I understand it, is
16 the same monetary value?

17 BY MR. VAUGHN:

18 Q. Correct.

19 A. I believe it would be.

20 Q. And what's the basis for
21 your opinion on that?

22 A. Because I don't see how it
23 substantially changed the effectiveness
24 of the drug.

1 Q. And what do you mean by the
2 effectiveness of the drug?

3 A. Its ability to do what it
4 was intended to do, which was control
5 heart failure, hypertension post-MI.

6 Q. And is it your opinion that
7 the levels of NDMA in generic valsartan
8 are unable to increase a person's risk of
9 developing cancer?

10 MS. THOMPSON: Objection.
11 Form.

12 THE WITNESS: I don't think
13 I'd characterize my opinion as
14 being unable. I don't think I
15 used those terms anywhere.

16 BY MR. VAUGHN:

17 Q. What is your opinion as to
18 if the levels of NDMA contained in
19 generic valsartan can increase the
20 levels -- increase the risk of someone
21 developing cancer?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: We don't have

1 the answer to that because we
2 don't have adequate data in humans
3 to make that determination.

4 BY MR. VAUGHN:

5 Q. If the levels of NDMA in
6 generic valsartan did increase the risk
7 of someone developing cancer, would you
8 agree that it would reduce the monetary
9 value of that medication?

10 MS. THOMPSON: Objection.
11 Form. He wasn't designated on
12 issues of monetary value. So
13 I'm --

14 MR. VAUGHN: He just said --
15 he just told me that he had an
16 opinion on it, so I'm exploring
17 that opinion.

18 THE WITNESS: Yeah, I don't
19 really -- it wasn't any of the
20 focus that I used in my
21 evaluation.

22 So I haven't really
23 expressed any kind of opinion on
24 monetary, other than I don't think

1 it would have altered its
2 effectiveness and not necessarily
3 another step of whatever that
4 monetary value would be.

5 BY MR. VAUGHN:

6 Q. Okay. So you do not plan to
7 tell the jury that the monetary value of
8 valsartan contaminated with NDMA is
9 unchanged?

10 A. I have no plans on talking
11 about monetary value.

12 Q. Okay. Do you think it's
13 acceptable for a patient to take generic
14 valsartan at the highest levels of
15 contamination of NDMA that we've seen?

16 MS. THOMPSON: Objection.
17 Form.

18 THE WITNESS: Well, again,
19 I'm not sure exactly what you're
20 asking.

21 What I have formed an
22 opinion on and provided in my
23 report is that I don't believe
24 there's any -- any risk associated

1 with the amount of NDMA that's in
2 any of the valsartan products that
3 I evaluated.

4 BY MR. VAUGHN:

5 Q. And what amount of NDMA
6 would be necessary in valsartan to
7 increase the risk of someone developing
8 cancer?

9 A. In humans, we don't have
10 that answer. We're having to completely
11 rely on animal data to make any kind of
12 extrapolation along those lines at all.

13 And I think we've seen in
14 the literature multiple people express
15 concerns about extrapolating animal data
16 to human data.

17 I did in my report try to
18 do, based on the available data with all
19 those known limitations, suggest that the
20 amount of what I'm going to call
21 impurities of NDMA in any of the
22 valsartan products seems well below what
23 in the animal studies might be expected
24 to cause any cancer.

1 Q. And so do you not have an
2 opinion as to how much NDMA it would take
3 to increase the risk of someone
4 developing cancer?

5 MS. THOMPSON: Objection.
6 Form. And again, this is not what
7 he was designated on.

8 THE WITNESS: Yeah, I don't
9 think that's what any focus on my
10 report was on.

11 MR. VAUGHN: Tyler, can you
12 pull up his expert report for me.

13 TRIAL TECH: Sure. Give me
14 one second.

15 (Document marked for
16 identification as Exhibit
17 Bottorff-1.)

18 MS. THOMPSON: We're giving
19 him a hard copy of his report as
20 well.

21 MR. VAUGHN: Sounds good.
22 Tyler, can we go to Page 63
23 of this report.

24 TRIAL TECH: Sure. And this

1 will be Exhibit 1.

2 MR. VAUGHN: Yeah. Thank
3 you for that.

4 TRIAL TECH: No problem.
5 You said Page 63?

6 MR. VAUGHN: Yeah.

7 BY MR. VAUGHN:

8 Q. And Dr. Bottorff, let me
9 know when you're there.

10 A. I am. I'm there now.

11 Q. Can you read looks like
12 Opinion VII..?

13 Can you read it out loud?
14 I'm sorry.

15 A. Yes, I will.

16 "The scientific literature
17 and evidence, which I have reviewed
18 extensively, do not support that the
19 valsartan products during the time period
20 at issue carried an independent risk of
21 cancer, nor that there is any increased
22 risk of cancer associated with the
23 valsartan containing the NDMA/NDEA
24 impurity as compared to valsartan with a

1 zero level of NDMA or NDEA."

2 Q. Okay. Would you agree with
3 me that you're giving an opinion that the
4 levels of NDMA do not increase the risk
5 of a patient's cancer?

6 A. Yes. But I thought your
7 question was, how much would it take to
8 cause cancer. And I didn't have a good
9 answer to that.

10 MS. THOMPSON: I was trying
11 to get an objection in there.

12 THE WITNESS: Oh, sorry.

13 MR. VAUGHN: So reminder to
14 give me a pause.

15 I was objecting to the form
16 of the last question.

17 THE WITNESS: Sorry.

18 BY MR. VAUGHN:

19 Q. Doctor, is it your opinion
20 that no level of NDMA would cause cancer
21 in a human?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: I don't know

1 the answer to that. We don't have
2 any data on what it would take to
3 cause cancer in humans with drugs
4 that haven't been -- or compounds
5 that haven't been studied in
6 humans.

7 BY MR. VAUGHN:

8 Q. If you do not know the level
9 that would -- of NDMA that it would take
10 to cause cancer, how can you give an
11 opinion that the levels of NDMA in
12 valsartan cannot increase the risk of
13 someone developing cancer?

14 MS. THOMPSON: Objection.
15 Form.

16 THE WITNESS: Again, as I
17 said before, we're having to
18 extrapolate the animal data with
19 all those known limitations.

20 And so, this statement was
21 based on how much NDMA did not
22 seem to cause cancer in animals.

23 And that was in many cases
24 way above the amount that's in any

1 of these valsartan products.

2 So again, accepting those
3 limitations, that's where this
4 conclusion comes from.

5 BY MR. VAUGHN:

6 Q. So you're not able to tell
7 our jury at what point -- at what level
8 NDMA in valsartan would increase the risk
9 of someone developing cancer?

10 A. Yeah. I don't think there's
11 anybody who can do that.

12 Q. What is the highest level of
13 NDMA that you're aware of in generic
14 valsartan?

15 A. I can look at my report,
16 which I think --

17 Q. Take your time.

18 A. No problem. Just scanning
19 through the NDMA amounts on Page 6, 7,
20 and 8 of my report, the highest amount, I
21 think, was just over 20 micrograms.

22 Q. So is it safe -- I'm sorry.

23 A. I was just going to add, in
24 a valsartan 320-milligram tablet.

1 Q. I appreciate that.

2 And so the opinions in your
3 expert report only apply to a daily NDMA
4 exposure level of 20 micrograms or lower?

5 MS. THOMPSON: Objection to
6 form.

7 THE WITNESS: Sorry. I'm
8 not -- that's not exactly what I
9 say in my report.

10 BY MR. VAUGHN:

11 Q. What is it -- how did I
12 mischaracterize it?

13 A. If we go to Page 32 and 33,
14 which is where I make that extrapolation
15 from -- this is one study, for example,
16 by Ito that there was an animal dose that
17 did not produce cancers, and
18 extrapolating that in kilogram to the
19 human exposure, if you use the same
20 milligram per kilogram calculation,
21 again, with all those limitations, then
22 the amount that was not cancer causing in
23 this study were anywhere from
24 approximately 300 to over 20,000 times

1 the amount that's in any of the valsartan
2 products.

3 Q. We'll get more into that in
4 a little bit. But in forming your expert
5 opinions, the highest level of NDMA that
6 you were aware of in valsartan was
7 20 micrograms, correct?

8 A. Correct.

9 MR. VAUGHN: Can we go to --
10 back to Page 6 real quick, Tyler.

11 BY MR. VAUGHN:

12 Q. All right. On that second
13 paragraph, Doctor, you note that there's
14 levels as high as 120 parts per million.
15 Where did that information come from?

16 A. I'm assuming that it's a
17 part per million conversion from these
18 data, from the FDA's laboratory analysis.

19 Q. Where did you find that data
20 though? Where did you find the 120 parts
21 per million? Are you the one that did
22 that calculation?

23 A. No. I wouldn't have done
24 the calculation.

1 Q. So where did you find that
2 information? I don't see a citation. So
3 I'm just wondering where this came from?

4 A. I don't recall exactly.

5 Q. What did you say ppm stands
6 for?

7 A. Parts per million.

8 Q. Okay. And you would expect
9 that that part per million, if you
10 actually do the math to figure out how
11 many micrograms that could be in a pill
12 of valsartan, would be no more than
13 20 micrograms, right?

14 A. If this range is
15 representative of what the FDA's analysis
16 is, then that would be correct.

17 Q. But you're not sure where
18 this range even comes from?

19 MS. THOMPSON: Objection to
20 form.

21 THE WITNESS: No.

22 Sorry.

23 My best guess at this point
24 in time is that those are the

1 ranges that were also in the FDA's
2 testing, but I don't recall it
3 exactly at this point.

4 BY MR. VAUGHN:

5 Q. Okay. Doctor, are you aware
6 how to convert parts per million into
7 micrograms or nanograms in a pill?

8 A. Yes, it's based on the
9 milligram strength of the tablet that
10 that's calculated.

11 Q. And how many nanograms --
12 are you aware of how many nanograms are
13 in a milligram?

14 A. Yes.

15 Q. How many?

16 A. A milligram has a thousand
17 micrograms, which also has a thousand
18 nanograms per microgram. So that would
19 be about a million.

20 Q. It would be one million?

21 A. Yes.

22 Q. And so for every milligram
23 of valsartan, there would be 120
24 nanograms of NDMA; is that correct?

1 A. I think that's the correct
2 calculation.

3 MR. VAUGHN: Tyler, can you
4 pull a calculator up for us.

5 BY MR. VAUGHN:

6 Q. All right. And how --
7 before we do this, 20 micrograms, how
8 many nanograms would that be?

9 A. 20,000.

10 Q. 20,000. Okay. So let's
11 take the 120 -- let me see if I can --
12 there we go. 120 was the parts per
13 million. Oh, didn't want that to happen.
14 120.

15 And what's the largest dose
16 of valsartan?

17 A. 320 milligrams.

18 Q. One second.

19 120 times -- did you say 320
20 was the largest?

21 A. Correct.

22 MR. VAUGHN: Hey, Tyler, can
23 you try and control this? It's
24 not working for me.

1 TRIAL TECH: Yeah, I think
2 you just need to clear -- do it
3 120.

4 MR. VAUGHN: Times 320.

5 TRIAL TECH: Where is --
6 okay, now it's clear. 120 times
7 320.

8 There you go.

9 BY MR. VAUGHN:

10 Q. That's 38,400 nanograms,
11 correct, Doctor?

12 A. Yes.

13 Q. And how many micrograms
14 would that be?

15 A. 38.4.

16 Q. And would you agree with me
17 that's approximately twice as high as any
18 of the levels the FDA identified?

19 MS. THOMPSON: Objection.
20 Form.

21 THE WITNESS: Yeah, so I'm
22 guessing that was ZHP's own
23 analysis and not the FDA's
24 analysis where that separate range

1 of 120 came from.

2 BY MR. VAUGHN:

3 Q. Did you review ZHP's
4 analysis?

5 A. I think it's -- I think it's
6 in my reliance documents.

7 Q. Okay. Do you remember any
8 levels higher than 120 parts per million
9 in ZHP's analysis?

10 A. I do not.

11 If you -- if I can just
12 expand a little bit. If I recall, ZHP's
13 analysis was based on the parts per
14 million of their API, which would be the
15 small amount of milligrams of the active
16 ingredient.

17 So I don't know if that
18 changes the calculation or not.

19 Q. Can you explain to me what
20 API is?

21 A. The active ingredient.

22 Q. And what's the active
23 ingredient in valsartan?

24 A. Valsartan.

1 Q. Okay. And the final pill,
2 what is it made up of besides valsartan
3 and sometimes NDMA and NDEA?

4 MS. THOMPSON: Objection to
5 form.

6 THE WITNESS: Off the top of
7 my head, I don't know that
8 exactly. But I can tell you,
9 having been trained in pharmacy,
10 that it will have all kinds of
11 binders and other excipients and
12 lubricants so it flows through
13 machines when they make the
14 tablets and that kind of thing.

15 BY MR. VAUGHN:

16 Q. So a 320-milligram valsartan
17 pill will have 320 milligrams of
18 valsartan in it, correct?

19 A. Correct.

20 Q. But will the total pill be
21 more than 320 milligrams because it has
22 other constituents in it?

23 A. It would have to be.

24 Q. Okay. And so if ZHP's parts

1 per million is on the API of valsartan,
2 how does that make a difference now when
3 we're going to the final pill if there's
4 still 320 milligrams in there?

5 A. It's part of the same part
6 per million calculation. But I don't
7 know how that changes when the API gets
8 incorporated in -- into the tablet.

9 Q. Okay. But the final tablet
10 would be more than 320 milligrams, right?

11 A. Right.

12 Q. Do you have any idea, like,
13 as a pharmacist, on average, what
14 percentage of a pill is filler?

15 A. I haven't looked at that
16 kind of calculation in, gosh, years,
17 because it's never really been called
18 into question or needed to be known.

19 Q. And so, in forming your
20 opinions in this litigation, you didn't
21 consider the amount of filler in
22 valsartan, correct?

23 MS. THOMPSON: Objection to
24 form.

1 THE WITNESS: Correct.

2 Sorry.

3 I did not.

4 BY MR. VAUGHN:

5 Q. If someone were to test a
6 pill, the parts per million would be
7 lower than if they tested the API,
8 correct?

9 A. You know, at this point I'm
10 not sure, because if it's based on the
11 320 milligrams of active ingredient,
12 seems like the calculation would still be
13 the same.

14 Q. Well, let's say a pill is
15 640 milligrams but only half of that is
16 valsartan, would that not half the parts
17 per million of the NDMA in the pill?

18 MS. THOMPSON: Objection to
19 form.

20 THE WITNESS: If you based
21 it on the weight of the actual
22 pill instead of based on the
23 active ingredient.

24 BY MR. VAUGHN:

1 Q. And if you didn't know the
2 percentages of what the filler were, what
3 would you -- how could you base it on
4 anything but the entire pill's weight?

5 A. Well, I think the issue at
6 hand was the part per million of the
7 valsartan and not the ppm based on any of
8 the excipients or anything else.

9 Q. So would you agree with me
10 that it would be more appropriate to use
11 the ppm of the API than the final
12 product?

13 A. I would agree with that.

14 MR. VAUGHN: Tyler, can we
15 go back to --

16 Can you guys all hear me?
17 It says my connection is unstable
18 right now.

19 Okay. Tyler can we go back
20 to Page 6 of this expert report.

21 Zoom out a little bit.

22 BY MR. VAUGHN:

23 Q. You note here, the fourth
24 column on the right, midpoint --

1 MR. VAUGHN: And if we go to
2 the next page, Tyler.

3 BY MR. VAUGHN:

4 Q. It looks like you calculated
5 the midpoint of the contamination; is
6 that correct?

7 MS. THOMPSON: Objection to
8 form.

9 THE WITNESS: Correct.

10 BY MR. VAUGHN:

11 Q. Why did you calculate the
12 midpoint?

13 A. It was an attempt to try to
14 represent that it would be unlikely over
15 the three to four or whatever years of
16 exposure at the time that these
17 impurities were known to be in valsartan
18 tablets that someone would take the exact
19 same lot for the entire period of time
20 that they were on that particular dose of
21 valsartan.

22 And so they would have, even
23 within the same manufacturer, probable
24 exposure to a different lot that had a

1 different amount and/or be switched over,
2 depending on what the pharmacy was
3 carrying at the time, to another product
4 that had a different amount.

5 So it was really just to try
6 to give an idea. You have the lowest
7 amount that could be found, which in many
8 cases was below the lower limits of
9 detection, and the highest amount that
10 was found in one of the products.

11 But the reality is that an
12 exposure value might actually be
13 something that's more of a midpoint.

14 Q. Do you know how the FDA came
15 to these results?

16 A. In terms of the analytical
17 process?

18 Q. Yeah. I mean, were they
19 testing the whole pill or were they
20 testing the API?

21 A. I think they could only have
22 been testing the full pill.

23 Q. And have you seen any
24 evidence that the FDA considered how much

1 filler is in the pill?

2 A. I've not seen that anywhere.

3 Q. A midpoint isn't the same as
4 the average, correct?

5 A. Correct. Which is why I did
6 not put the average in there, is you
7 don't have the raw data to be able to
8 accurately calculate an average.

9 Q. Did the defense attorneys
10 not provide you the raw data?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: No. I went
14 off this, which was the FDA's
15 report. And if you don't have
16 each individual result for each
17 individual tablet, and you just
18 have an upper and lower limit of
19 the range, you can't guesstimate
20 how many that was involving to be
21 able to calculate statistically an
22 average.

23 BY MR. VAUGHN:

24 Q. Did you not ask defense

1 counsel to provide you all the levels of
2 the internal testing?

3 MS. THOMPSON: Objection.
4 Form.

5 THE WITNESS: I did not.

6 BY MR. VAUGHN:

7 Q. Why?

8 A. I had no reason to.

9 Q. I'm sorry. You didn't
10 consider any of the internal testing in
11 forming your opinions?

12 MS. THOMPSON: Objection.
13 Form.

14 THE WITNESS: No. That is
15 in my report. It is what I
16 considered for the amounts
17 contained in the valsartan
18 products.

19 BY MR. VAUGHN:

20 Q. What if the internal testing
21 shows much higher levels than this?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: I don't have

1 that data, so I don't know.

2 BY MR. VAUGHN:

3 Q. So your opinions won't apply
4 to it if the -- to the levels if they
5 were higher than what's in the FDA's?

6 A. It would depend how much
7 higher. And I'd have to see them.

8 Q. How much higher?

9 A. I don't know. I'd have to
10 see it.

11 Q. You said it depends on how
12 much higher. At what point does it
13 matter?

14 MS. THOMPSON: Objection.
15 Form.

16 THE WITNESS: Again, I'd
17 have to see them and then be able
18 to make that determination.

19 BY MR. VAUGHN:

20 Q. Is there any level that
21 you're going to say is unacceptable?

22 MS. THOMPSON: Objection
23 form.

24 THE WITNESS: I believe

1 you've asked that, and my answer
2 was I don't think there is a level
3 that I can say is going to be
4 related to cancer in humans,
5 because we don't know that. We
6 don't have that data.

7 BY MR. VAUGHN:

8 Q. So it's irrelevant to you
9 how much NDMA is in valsartan?

10 MS. THOMPSON: Objection.
11 Form. Mischaracterizes testimony.

12 THE WITNESS: Yeah, I don't
13 think I ever used the word
14 "irrelevant."

15 BY MR. VAUGHN:

16 Q. Is there any point when you
17 would be concerned on the level of NDMA
18 in valsartan?

19 MS. THOMPSON: Objection.
20 Form.

21 THE WITNESS: Yeah, I don't
22 really know what you're trying to
23 get me to say or what you're
24 really asking.

1 I'm concerned with the
2 amounts that I know, based on the
3 FDA's analysis, were in valsartan
4 tablets, and then comparing that
5 to the animal data, which is all
6 we have, to see if I believe that
7 this exceeded the metabolic
8 capacity -- and this is from a
9 pure pharmacokinetic drug
10 metabolism standpoint -- that has
11 been associated in animal studies
12 with not causing cancer.

13 So I wasn't looking to try
14 to establish an amount that would
15 cause cancer. So I don't have an
16 opinion on that.

17 BY MR. VAUGHN:

18 Q. You weren't trying to figure
19 out how much NDMA it would take to cause
20 cancer in humans?

21 A. No. I was not.

22 Q. Okay. And in forming your
23 opinions, you assumed that the FDA's
24 analysis is actually the highest levels

1 of NDMA engineered in valsartan, correct?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I did not

5 assume that.

6 BY MR. VAUGHN:

7 Q. So you think that there
8 might be actually higher levels than the
9 FDA is aware of?

10 MS. THOMPSON: Objection to
11 form.

12 THE WITNESS: I don't know.
13 This is what I had to go off of,
14 based on the FDA's published data.

15 BY MR. VAUGHN:

16 Q. So why is that not assuming
17 the highest levels? You didn't even ask
18 for the internal data.

19 A. I wasn't assuming anything.
20 I was evaluating what I had access to.

21 Q. Doctor, were you initially
22 retained for this litigation by Teva?

23 A. No one from Teva has ever
24 contacted me.

1 Q. Were you initially retained
2 for this litigation for every defendant
3 or a specific defendant?

4 A. I think when I was
5 originally retained, the word Teva may
6 have been mentioned in some of those
7 early communications. But since then
8 there's never been any contact directly
9 with Teva at all.

10 Q. Okay. So you do think you
11 might have initially been retained by
12 Teva?

13 A. No. I didn't say that.
14 I've only been retained by
15 GT. And they may have mentioned that
16 Teva was one of the defendants in some of
17 the earlier communication. But since
18 then, I understand that there are other
19 defendants in this as well.

20 Q. When were you initially
21 retained for this litigation?

22 A. It was either right at the
23 end of 2020 or the very early part of
24 2021.

1 Q. And approximately when did
2 you become aware of all the other
3 defendants?

4 A. I -- I don't have a date for
5 that. Probably sometime in the spring.

6 MR. VAUGHN: Okay. Tyler,
7 can we go to -- I think it's
8 Exhibit B on my files. It's -- or
9 exhibit -- one second. Yeah,
10 Exhibit B of his expert report.

11 And then can we go to
12 Page 10.

13 (Document marked for
14 identification as Exhibit
15 Bottorff-2.)

16 BY MR. VAUGHN:

17 Q. All right. We'll see down
18 here some Teva Bates numbers.

19 MR. VAUGHN: And then,
20 Tyler, can we go to the next page.

21 BY MR. VAUGHN:

22 Q. And then a bunch more Teva
23 Bates numbers.

24 MR. VAUGHN: Next page,

1 Tyler.

2 BY MR. VAUGHN:

3 Q. A bunch more Teva.

4 MR. VAUGHN: Next page.

5 BY MR. VAUGHN:

6 Q. A bunch more Teva.

7 MR. VAUGHN: Next page.

8 BY MR. VAUGHN:

9 Q. All Teva again.

10 MR. VAUGHN: Next page.

11 BY MR. VAUGHN:

12 Q. And then there's two other
13 Bates numbers here. There's HLL. Do you
14 know what the HLL Bates numbers denote,
15 Doctor?

16 A. Is that on this screen that
17 I'm looking at?

18 Q. Yeah. The top right-hand
19 corner. It's the only ones that didn't
20 have a Teva Bates number. I didn't know
21 if you knew what company's documents
22 those two are.

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: I -- I assume
2 they're associated with what's on
3 the left hand column.

4 BY MR. VAUGHN:

5 Q. Okay. So did you only
6 review internal documents of Teva in this
7 litigation?

8 MR. VAUGHN: Is that my
9 internet or his that's messing up?
10 He's frozen on my screen.

11 THE VIDEOGRAPHER: He looks
12 frozen on my screen.

13 THE WITNESS: Oh, well.

14 THE VIDEOGRAPHER: Oh, yeah,
15 he's back.

16 BY MR. VAUGHN:

17 Q. Okay. I'm sorry, Doctor. I
18 missed whatever your answer was.

19 A. I didn't yet because you
20 said I was frozen so --

21 Q. Okay.

22 A. -- I didn't think you could
23 hear me either.

24 Q. I appreciate it.

1 A. In looking at these
2 documents, my recollection back then, I
3 think the first round of materials that
4 were provided to me were probably Teva
5 materials.

6 Q. Were any of those internal
7 testing by Teva?

8 A. They may have been. I don't
9 recall specifically.

10 Q. You didn't review any other
11 documents of any other defendant besides
12 Teva, did you?

13 A. No, I don't believe so.

14 Q. Why did you only review Teva
15 documents?

16 A. The question that I was
17 specifically addressing didn't seem to be
18 as important to be looking at internal
19 documents for every single defendant as
20 opposed to evaluating the literature for
21 NDMA, NDEA metabolism and distribution.

22 Q. Well, then why did you
23 review Teva documents?

24 MS. THOMPSON: Objection.

1 Form.

2 THE WITNESS: They were sent
3 to me early on. And when I
4 receive documents, I reviewed
5 them.

6 BY MR. VAUGHN:

7 Q. Are these the documents that
8 you requested, or they just picked out
9 documents and sent to you?

10 MS. THOMPSON: Objection to
11 form.

12 THE WITNESS: I didn't
13 request them, so they were somehow
14 selected and sent to me.

15 MR. VAUGHN: We can take
16 down the exhibit. I'm done with
17 that for now.

18 BY MR. VAUGHN:

19 Q. Doctor, what degrees do you
20 hold?

21 A. I hold a bachelor's degree
22 from Georgia Tech, and PharmD degree from
23 the University of Kentucky.

24 Q. You're a pharmacist?

1 A. Yes.

2 Q. When you're filling a
3 medication for someone, what do you call
4 that person that you're filling the
5 medication for? For instance, are they
6 your client, a customer, a patient?

7 A. Well, they would be a
8 patient in my reference. But that's not
9 been what my career has been, is filling
10 prescriptions, that type of pharmacist.

11 Q. Have you ever filled a
12 prescription?

13 A. Yes.

14 Q. When was the last time that
15 you did that?

16 A. Probably the summer of 1982.

17 Q. If you're not filling
18 prescriptions, what is it that you do for
19 work?

20 A. My career has always been in
21 academic pharmacy. So certainly teaching
22 has been part of that. But as part of
23 that, I had a clinical practice where I
24 rounded with an interdisciplinary

1 cardiology team on inpatients at academic
2 medical centers for 35 years.

3 Q. What do you currently do for
4 work?

5 A. What I thought was going to
6 be a semi-state of retirement has turned
7 out to be almost full-time, because I'm
8 continuing to teach for my most recent
9 academic appointment at Manchester
10 University in Fort Wayne, Indiana. And
11 certainly Covid has allowed a lot of
12 online teaching to be done, so I didn't
13 have to be in Indiana all the time to do
14 that.

15 And then I -- the position
16 that I was in prior to that was in
17 Knoxville at South College. And I'm now
18 chair of their independent research
19 committee.

20 And then most recently I've
21 been added to the adjunct faculty the
22 University of Cincinnati where I used to
23 teach for 20 years to be involved in
24 their online Masters in pharmacogenomics

1 program.

2 Q. At Manchester University,
3 are you a professor or an adjunct
4 professor?

5 A. As of last August, I am
6 adjunct. And I was professor for five
7 years prior to that.

8 Q. What is an adjunct
9 professor? What's the difference of that
10 and a professor?

11 A. A pay cut basically.
12 You know, going to some more
13 of what would be called a part-time
14 status. Still paid, but part-time
15 status.

16 Q. Okay. How many hours a week
17 are you -- do you devote to the adjunct
18 professor?

19 A. For Manchester, probably 15.
20 For University of Cincinnati probably
21 five to ten depending on when things are
22 being done that are -- or what I'm being
23 expected to do.

24 Q. How many students do you

1 currently teach?

2 A. There are roughly 65 in each
3 class of the four years of pharmacy
4 students at Manchester. And the online
5 genomics program has just started at
6 Cincinnati, so it is a smaller program.
7 I think it has like eight to ten.

8 Q. Okay. What is
9 pharmacogenomics? Can you explain that?

10 A. Yeah. It's the study of the
11 interaction between genetic alterations
12 in drug metabolism or response and the
13 drugs that are being given to patients.

14 So it is a component of sort
15 of a common buzzword these days called
16 personalized medicine.

17 Q. And so is the focus on it
18 specifically pharmacological drugs, not
19 carcinogens?

20 A. All drugs.

21 Q. Are there drugs that are
22 carcinogens?

23 A. Yes.

24 Q. Such as?

1 A. Immunosuppressant drugs for
2 transplant patients have the ability to
3 induce cancers by blocking cancer sort of
4 surveillance systems.

5 Q. How do they block cancer
6 surveillance systems?

7 A. They're immunosuppressants.
8 And as part of the immune system is a
9 component of it that suppresses cancer
10 cells.

11 Q. So would you agree with me
12 that an immunosuppressant increases the
13 risk of one developing cancer?

14 A. Yep. That's been reported.

15 MS. THOMPSON: Sorry, we
16 have a loud air conditioner.
17 Hopefully it will turn off soon.

18 MR. VAUGHN: I can't hear it
19 actually.

20 MS. THOMPSON: It's loud in
21 here.

22 MR. VAUGHN: Can we go back
23 to the expert report, Tyler.

24 Page 3.

1 BY MR. VAUGHN:

2 Q. All right. You note during
3 your career that you have served on
4 advisory boards and national speaking
5 bureaus for several pharmaceutical
6 companies that make sartans, including
7 Merck -- should that be losartan?

8 A. Yeah.

9 Q. And Bristol-Myers Squibb,
10 irbesartan, and Novartis, valsartan.
11 Were those paid positions?

12 A. Yes. Being on speakers
13 bureaus, you're asked to give
14 presentations and be paid for those when
15 you go.

16 Q. Approximately in what years
17 were you paid by these pharmaceutical
18 companies?

19 A. Merck was the first sartan
20 company on the market. So that would
21 have been maybe in the mid to late '90s,
22 irbesartan sort of in the late '90s, and
23 valsartan, late '90s early 2000. But I
24 haven't been on the speaker bureaus for

1 over 20 years.

2 Q. Have you done work for
3 pharmaceutical companies within the last
4 20 years?

5 A. What do you mean by work?

6 Q. Have you been paid by
7 pharmaceutical companies in the last
8 20 years outside of litigation?

9 A. A little bit. You know, if
10 you keep up with what's happened in
11 pharma and speaker bureaus, there's
12 really been a pretty strict federal limit
13 on what they used to do.

14 So I am on a couple speaker
15 bureaus now, But for neither one of those
16 companies have I given a talk in the last
17 18 months because they shut those down
18 for Covid.

19 Q. Are there any other
20 pharmaceutical companies that make
21 sartans that you have been paid by
22 previously, besides the ones listed here?

23 A. No.

24 Q. How many types of sartans

1 are there?

2 A. Structural differences or in
3 that whole category of sartans, how many
4 of them?

5 Q. In the category of sartans.

6 A. I think there's eight or
7 nine.

8 Q. Can you name off the ones
9 that you recall?

10 A. Oh, there's these three.
11 There's eprosartan. I'd have to look at
12 a list. These are by far the more common
13 used though.

14 Q. The eight or nine types of
15 sartans, how many have been found to have
16 lots that are contaminated with NDMA or
17 NDEA?

18 MS. THOMPSON: Objection.
19 Form.

20 THE WITNESS: To my
21 knowledge, these three. So I've
22 not really looked into the other
23 ones.

24 BY MR. VAUGHN:

1 Q. And so would you agree that
2 there are numerous sartans that are not
3 contaminated with NDMA or NDEA?

4 A. I don't know about numerous,
5 but I think there's some.

6 Q. Do you think there's more
7 than there are that are contaminated?

8 MS. THOMPSON: Objection to
9 form.

10 THE WITNESS: I don't have a
11 breakdown because I haven't looked
12 at the other ones that much.

13 BY MR. VAUGHN:

14 Q. Okay. So there's eight or
15 nine types of sartans, and at least three
16 of them that you're aware of are
17 contaminated with a carcinogen, correct?

18 MS. THOMPSON: Objection to
19 form.

20 THE WITNESS: Correct.

21 BY MR. VAUGHN:

22 Q. And you didn't consider the
23 other sartans in forming your opinions in
24 this litigation, correct?

1 A. Correct. I did not.

2 Q. And so the whole
3 risk/benefit analysis thing that you're
4 talking about in your report, you didn't
5 consider the fact that there's sartans on
6 the market that aren't contaminated with
7 a carcinogen?

8 MS. THOMPSON: Objection to
9 form.

10 THE WITNESS: No. I would
11 say that's part of my
12 consideration, is that there were
13 potential alternatives for these
14 three.

15 BY MR. VAUGHN:

16 Q. How many pharmaceutical
17 companies make sartans?

18 A. I guess now that many of
19 them are generic, there could be as many
20 as two dozen. I don't know for sure.

21 Q. How many pharmaceutical
22 companies make valsartan?

23 A. I don't have an exact
24 number. I would say maybe as many as

1 ten.

2 Q. Can you list off the name of
3 all the defendants in this litigation?

4 MS. THOMPSON: Objection.

5 Form.

6 BY MR. VAUGHN:

7 Q. Sorry. Let me rephrase
8 that.

9 Can you list off all of the
10 defendants who manufacture valsartan?

11 A. Well, I don't know if it's
12 the same as what I used, which is the
13 FDA's list of valsartan products
14 containing the NDMA or NDEA. But I could
15 read those off if that's what you would
16 like.

17 Q. No. That's okay. But your
18 opinion is that it doesn't matter the
19 manufacturer, none of the levels of NDMA
20 in valsartan are going to increase
21 someone's risk of cancer?

22 MS. THOMPSON: Objection.

23 Form.

24 THE WITNESS: Could you ask

1 that again? I want to be sure I
2 answer it right.

3 BY MR. VAUGHN:

4 Q. Is it your opinion that it
5 doesn't matter who the manufacturer is of
6 the generic valsartan that contains
7 levels of NDMA; it's not going to
8 increase someone's risk of cancer?

9 MS. THOMPSON: Objection.
10 Form.

11 THE WITNESS: The
12 manufacturer played no role in any
13 of my analyses. It was only the
14 amount of NDMA or NDEA that
15 factored into my analyses.

16 BY MR. VAUGHN:

17 Q. But you -- so the amount of
18 NDMA did factor into your analysis, but
19 you're not sure if you're aware of the
20 highest levels, correct?

21 A. I'm sure that no one knows
22 what the highest levels would be.

23 Q. Would you want to know if
24 there are levels higher than you're

1 aware -- than you are aware of in your
2 report?

3 MS. THOMPSON: Objection to
4 form.

5 THE WITNESS: I suppose. If
6 I had that, I could redo my
7 calculations and my opinions. But
8 this is what I worked off of.

9 BY MR. VAUGHN:

10 Q. If defense counsel was aware
11 of levels higher than what you worked off
12 of, do you think that they would have
13 given you that information?

14 MS. THOMPSON: Objection.
15 Form. Calls for speculation.

16 THE WITNESS: I have no
17 idea.

18 BY MR. VAUGHN:

19 Q. Would you have expected them
20 to give you that information?

21 MS. THOMPSON: Same
22 objection.

23 THE WITNESS: I guess so.

24 BY MR. VAUGHN:

1 Q. Is there a brand name of
2 valsartan?

3 A. Diovan.

4 Q. Can you say that again? The
5 audio broke -- cut out.

6 A. I'm sorry. The originator
7 was --

8 Q. I'm not -- you're frozen and
9 no audio.

10 A. Hmm.

11 Q. Oh, you're back.

12 A. Okay. The originator was
13 Diovan with Novartis.

14 Q. Is that still on the market?

15 A. I think so.

16 Q. And are you aware if the
17 brand name Diovan has NDMA or NDEA in it?

18 MS. THOMPSON: Objection.

19 Form.

20 THE WITNESS: I'm not aware
21 specifically.

22 BY MR. VAUGHN:

23 Q. And so you're not aware if
24 it's ever had it in it?

1 A. I am not. And I know a lot
2 of times what the originators do when the
3 drug goes generic, is they either stop it
4 totally or they actually get generic drug
5 from somebody else and make their own
6 generic. And I don't know specifically
7 if they've done that or not.

8 Q. You haven't looked into that
9 in this litigation, did you?

10 A. I did not.

11 Q. So you have no idea if the
12 brand name has always been completely
13 clean of carcinogens?

14 MS. THOMPSON: Objection.
15 Form.

16 THE WITNESS: I -- I don't
17 know that anybody knows that.

18 BY MR. VAUGHN:

19 Q. Do you know if the
20 manufacturing process is different?

21 A. I didn't look into that. So
22 I don't.

23 Q. So as a nurse I have an
24 ethical obligation -- had an ethical

1 obligation to patients. And, you know, a
2 doctor has an patient relationship, and
3 that carries certain ethical obligations.

4 Are there similar type
5 ethical obligations a pharmacist has to
6 the person whose medication they are
7 filling?

8 MS. KAPKE: This is Kara
9 Kapke. Object to form.

10 MR. VAUGHN: Are you all --
11 I'm sorry.

12 Are all the defense
13 attorneys going to be objecting or
14 just one of them?

15 MS. THOMPSON: She, I
16 believe, represents a retailer
17 who's not part of the manufacturer
18 group. So --

19 MR. VAUGHN: Okay. I
20 appreciate the clarification.

21 BY MR. VAUGHN:

22 Q. So, Doctor, do pharmacists
23 have any type of ethical obligations to
24 the person whose medication they are

1 filling?

2 A. Every professional has an
3 ethical obligation.

4 Q. Can you go over -- go ahead.

5 A. It's part of the definition
6 of being a professional.

7 Q. Can you go through some of
8 those ethical obligations with me that a
9 pharmacist would have to a person who's
10 filling their medication?

11 MS. KAPKE: Object to form.

12 MS. THOMPSON: Same
13 objection.

14 THE WITNESS: Following the
15 laws, you know, being honest,
16 accurate. I'm not sure what
17 you're getting at.

18 BY MR. VAUGHN:

19 Q. Is informed consent part of
20 the relationship a pharmacist has with a
21 patient?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: In my

1 professional career, informed
2 consent is a document in a
3 clinical trial that a patient
4 signs that they understand and
5 have been aware of the risks and
6 the benefits of being involved in
7 that clinical trial.

8 So I don't -- I don't see
9 informed consent in what my daily
10 practice was, in that term.

11 BY MR. VAUGHN:

12 Q. Is that because you don't
13 actually fill medications for patients?

14 A. I wouldn't say it's for that
15 reason. That's just not how informed
16 consent is used.

17 Q. Do you not discuss informed
18 consent at all with your pharmacy
19 students?

20 A. In courses where I've taught
21 the process of conducting clinical trials
22 I have.

23 Q. If a pharmacist is aware
24 that one medication contains a carcinogen

1 and another version of that same
2 medication does not contain a carcinogen,
3 should they warn the patient about that?

4 MS. KAPKE: Object to form.

5 THE WITNESS: I mean, again,
6 in your hypothetical, you're
7 supposing that they know this.
8 And so if someone were to ask me
9 or you in your former practice --
10 you said you were a nurse?

11 BY MR. VAUGHN:

12 Q. Correct.

13 A. In your hypothetical that
14 you had two compounds, one that was a
15 known carcinogen, which is not what we're
16 talking about here, and one that was, and
17 one that wasn't, you know, would you go
18 ahead and give them the one that was? I
19 mean, I don't think anybody would answer
20 that they would do that.

21 Q. What about probable
22 carcinogen?

23 MS. THOMPSON: Objection to
24 form.

1 THE WITNESS: You know, I
2 don't -- I don't know that that
3 changes.

4 I think I would have to look
5 at the data to see if I agreed
6 with it.

7 BY MR. VAUGHN:

8 Q. What if a top cancer
9 researcher is the one that thinks that
10 the levels are high enough to increase
11 someone's risk of cancer?

12 Would you as a pharmacist
13 defer to a top cancer researcher?

14 MS. THOMPSON: Objection.
15 Form.

16 THE WITNESS: Again, I
17 haven't practiced in a drug store
18 setting in over probably 35 years.
19 So I don't know how that
20 information, if it were available,
21 would actually reach the
22 individual everyday practicing
23 pharmacist.

24 BY MR. VAUGHN:

1 Q. So you don't know if there's
2 a computer system that, like, notifies
3 the pharmacist, hey, this drug has a
4 carcinogen in it?

5 MS. KAPKE: Object to form.

6 THE WITNESS: Sorry. I'm
7 pretty sure that's not the case.

8 BY MR. VAUGHN:

9 Q. Okay. If you were aware of
10 literature that said the amount of a
11 carcinogen in a medication would increase
12 the risk of someone developing cancer,
13 would you let the patient know that?

14 MS. KAPKE: Object to form.

15 MS. THOMPSON: Same
16 objection.

17 THE WITNESS: Well, it's not
18 done at that level where that
19 responsibility is put in the hands
20 of an individual practicing
21 pharmacist.

22 Those decisions get made at
23 corporate levels or at regulatory
24 levels, not at the -- not at the

1 level of an individual practicing
2 pharmacist.

3 BY MR. VAUGHN:

4 Q. What do you mean by
5 corporate level?

6 A. Well --

7 MS. KAPKE: Sorry, Doctor.
8 This is Kara Kapke again. I'm
9 just going to interpose an
10 objection to this entire line of
11 questioning. This witness has
12 been designated on general
13 causation issues, not liability
14 issues.

15 And there's been an
16 agreement that the experts at this
17 stage of the litigation are only
18 testifying and will only be
19 questioned about liability
20 issues -- or only about causation
21 issues, and they will not be asked
22 about for -- designated on
23 liability issues.

24 And so I think this entire

1 line of questioning is improper
2 and in violation of the agreement
3 that has been made and -- among
4 the plaintiff and defendants.

5 MR. VAUGHN: I note your
6 objection. And just for the
7 record I'm trying to fully explore
8 the opinions that are within his
9 expert report.

10 Tyler, can we go back to his
11 expert report, I guess. Let's go
12 to Page 21.

13 MS. THOMPSON: And on that
14 line, I mean, if you're going to
15 talk about specific items in his
16 report, that's fine. But I don't
17 think anything about the ethical
18 obligations of a dispensing
19 pharmacist is in the report.

20 MR. VAUGHN: That's fine.

21 BY MR. VAUGHN:

22 Q. Here in the bottom of that
23 first paragraph, you note the risks --
24 you need to balance the risks and

1 benefits, that being the cornerstone --

2 MR. VAUGHN: Sorry, one
3 above that, Tyler. Yeah, the very
4 last sentence there.

5 BY MR. VAUGHN:

6 Q. "The balance of risk/benefit
7 is the cornerstone of therapeutic
8 decisionmaking."

9 That sounded a whole lot
10 like -- to me like informed consent.

11 Does that not sound like
12 informed consent to you, Doctor?

13 MS. THOMPSON: Objection.
14 Form.

15 THE WITNESS: No. As I said
16 before, informed consent is -- in
17 my professional experience, has
18 been used in the context of
19 enrolling a patient in a clinical
20 trial where there's a consent form
21 that they're asked -- that has to
22 be approved by an investigational
23 review board.

24 And that's -- I'm not sure

1 that we're using the same
2 terminology on what informed
3 consent is.

4 BY MR. VAUGHN:

5 Q. Okay. And so that informed
6 consent that you're talking about in a
7 clinical trial, what all does it have to
8 disclose?

9 A. The procedures of the study,
10 the amount that they're being reimbursed
11 for participating in the trial, the
12 nature of the drug, whether it's
13 experimental or not, those kind of
14 things.

15 Q. What does that have to --
16 this says decisionmaking, though, in your
17 opinion. What does what you just said
18 have to do with decisionmaking?

19 A. It doesn't. That's why I
20 was saying the use of the term "informed
21 consent" is not what this is.

22 Q. Okay. So you don't think
23 that a patient needs to be aware of all
24 risks and all benefits in order to obtain

1 informed consent?

2 MS. KAPKE: Object to form.

3 MS. THOMPSON: Object to
4 form.

5 THE WITNESS: Again,
6 therapeutic decisionmaking is
7 different from informed consent.
8 So I think that you're using it in
9 a context that it's not typically
10 used in.

11 BY MR. VAUGHN:

12 Q. Okay. So for therapeutic
13 decisionmaking when we're talking about
14 the risk and the benefit, would one of
15 the risks be what the level of NDMA is in
16 a pill?

17 A. I think you would have to
18 assess that risk and decide if there was
19 one or not.

20 Q. What other risk -- when
21 taking valsartan, besides how much of a
22 carcinogen in it, what are the other
23 risks that would go into this therapeutic
24 decisionmaking?

1 A. Well, first let me -- let me
2 say that using the term "carcinogen"
3 is -- it's a probable carcinogen in
4 humans. We don't have the data that it's
5 a for sure carcinogen.

6 Drugs have all kinds of
7 risks, particularly sartans.
8 Hyperkalemia, hypotension, renal
9 dysfunction. So the -- a rare case of
10 angioedema.

11 Those are the kind of risks
12 that you typically consider when you're
13 talking about therapeutic decisionmaking.

14 Q. Of those potential
15 complications that you just listed, would
16 you consider any of those or the
17 development of cancer to be a bigger risk
18 to the patient?

19 MS. THOMPSON: Objection.
20 Form.

21 THE WITNESS: Well, if the
22 question is, is cancer worse than
23 hyperkalemia, then I would say
24 yes, it is.

1 BY MR. VAUGHN:

2 Q. And so would it not be very
3 important to know the levels of a
4 potential carcinogen in a medication and
5 evaluating the risk/benefit of that
6 medication?

7 MS. THOMPSON: Objection.

8 MS. KAPKE: Object to form.

9 THE WITNESS: Yeah, again, I
10 think we're getting back into this
11 liability issue that is not what I
12 was considering.

13 I was looking at the
14 metabolism and distribution of
15 NDMA and NDEA.

16 And by putting this comment
17 in my statement or in my report,
18 it was more to remind people that
19 when the risk is unknown, which is
20 what I consider it to be, unknown
21 in humans, you also have to
22 remember stopping drugs in
23 patients is not without risk as
24 well.

1 And that's been clearly
2 identified in all of the FDA
3 reports that I've seen.

4 BY MR. VAUGHN:

5 Q. Doctor, why are there no
6 studies of NDMA in humans?

7 A. Why are there no studies?

8 Q. Yeah.

9 A. I'm not sure.

10 Q. Would it be ethical to give
11 humans NDMA and study what happens?

12 MS. THOMPSON: Objection.
13 Form. Outside the scope.

14 THE WITNESS: I think it
15 depends on the amount.

16 BY MR. VAUGHN:

17 Q. So you think the regulatory
18 agencies would approve a study on a
19 probable carcinogen in humans?

20 MS. THOMPSON: Objection to
21 form. Outside the scope.

22 THE WITNESS: Yeah, I don't
23 know. I think it would depend on
24 the amount, but I don't know.

1 BY MR. VAUGHN:

2 Q. Okay. So in forming your
3 opinions, you did not consider any human
4 data regarding NDMA exposure, correct?

5 A. That is not correct.

6 Q. I thought you said that
7 there wasn't any.

8 A. I think what I said is that
9 there were no data in humans showing that
10 it was a carcinogen. Or --

11 Q. What's -- go ahead.

12 A. I'm sorry. Or proving that
13 it was a carcinogen.

14 Q. Okay. What studies did you
15 look at in humans then that you are
16 opining didn't show it can cause cancer?
17 Because I didn't see that in your expert
18 report.

19 A. Let's go to Pages 48 through
20 end of 55, 56.

21 I did review the
22 epidemiology studies that have been done.

23 Q. Okay.

24 A. Either environmental or

1 dietary.

2 And let me be clear about
3 what my reason for putting that in my
4 report was.

5 I wasn't attempting to
6 individually critique or support any one
7 of these studies.

8 The purpose of putting them
9 in my report is that I saw some plaintiff
10 experts that looked at these same data
11 and were pretty confident in stating that
12 this proves that NDMA causes cancer.

13 And I look at the same
14 data -- and again, without getting into
15 discussion of odds ratios and confidence
16 limits, I didn't see a consistency in
17 these data that led me to the same
18 conclusion.

19 And so I thought it was
20 worth putting in my report that two
21 people or more looking at these same data
22 might not necessarily draw the exact same
23 conclusion.

24 Q. Would you agree that these

1 studies in humans at least identify what
2 organs NDMA could impact, if it went
3 systemically?

4 MS. THOMPSON: Objection.
5 Form.

6 THE WITNESS: I don't think
7 so. Because I don't think this
8 proves anything.

9 BY MR. VAUGHN:

10 Q. Why?

11 A. Because of their
12 inconsistency, some of their limitations
13 that, again, that others have commented
14 on. You know, if this proved that it was
15 definitely a human causing cancer
16 substance, then it would have had a
17 different level of designation in the
18 IARC.

19 Q. When you say prove, what
20 level of evidence is that? Is that like
21 more likely than not, like 51 percent,
22 75 percent? Do you have to get to
23 100 percent to get to prove?

24 A. I don't know. I don't have

1 an opinion on that level.

2 My comment more is that
3 there's inconsistency in the data. And
4 so I don't know what that cut point ought
5 to be.

6 Q. So is it your opinion that
7 every single study must say that NDMA
8 causes cancer in order to prove that it
9 causes cancer?

10 MS. THOMPSON: Objection.
11 Form. Mischaracterizes.

12 THE WITNESS: Yeah, that's
13 not what I'm saying.

14 What I'm saying is these
15 data look inconsistent enough to
16 me that I would not be willing to
17 draw the conclusion that we have
18 proof that NDMA causes cancer in
19 humans based on these epidemiology
20 trials and their limitations and
21 their inconsistencies.

22 MR. VAUGHN: We've been
23 going for a little over an hour.
24 Now is a decent time for a break

1 if you guys want to take one.

2 MS. THOMPSON: That's fine
3 with us.

4 MR. VAUGHN: All right.
5 Want to do --

6 THE VIDEOGRAPHER: The time
7 right now is 10:06 a.m. We're off
8 the record.

9 (Short break.)

10 THE VIDEOGRAPHER: The time
11 right now is 10:20 a.m. We're
12 back on the record.

13 BY MR. VAUGHN:

14 Q. Doctor, do you have any
15 programs open on your computer except for
16 Zoom?

17 A. No.

18 Q. And you'll keep it that way
19 for the whole deposition?

20 A. Yes.

21 Q. Great. A second ago you
22 said human studies did not prove that
23 NDMA causes cancer in humans. Doctor, do
24 you agree, though, that at least some of

1 the studies in humans where they gave
2 them NDMA or where they were exposed to
3 NDMA, that they found an association
4 between increasing levels of NDMA and
5 increasing rates of cancer?

6 MS. THOMPSON: Objection.
7 Form.

8 THE WITNESS: Yes, some of
9 those studies did show a
10 statistical association.

11 BY MR. VAUGHN:

12 Q. And was that cancer that
13 they found an association with NDMA, was
14 that specific to a certain organ?

15 A. No.

16 Q. What organs do you recall
17 being associated with NDMA being able to
18 incite cancer?

19 MS. THOMPSON: Objection.
20 Form.

21 THE WITNESS: Well, again,
22 the association was in differing
23 studies, different organs. They
24 looked at almost anything that you

1 can imagine. So it's sort of all
2 over the board.

3 BY MR. VAUGHN:

4 Q. There's a lot of organs that
5 NDMA is associated with causing cancer in
6 these studies?

7 A. There were many different
8 organs, yes. Again, I would add that it
9 wasn't necessarily within an individual
10 organ that it was always consistent that
11 it did show the association.

12 Q. Doctor, your audio cut out
13 again.

14 A. I'm sorry. What I was
15 adding was that in many cases when you
16 looked at a specific organ, for example,
17 you might find inconsistent results that
18 one study would find an association and
19 another study would not.

20 Q. Doctor, how many hours did
21 you spend in coming to your opinions
22 within your expert report?

23 A. I'd have to look at the two
24 invoices that I have sent. I'm guessing

1 somewhere around 100 to 120, something
2 like that.

3 MR. VAUGHN: Tyler, can we
4 go back to Exhibit B of his expert
5 report.

6 And can we go to the next
7 page.

8 BY MR. VAUGHN:

9 Q. Doctor, can you read off the
10 names of all plaintiff expert reports
11 that you reviewed?

12 A. Not off the top of my head,
13 but I certainly did review these that you
14 see on my list.

15 MS. THOMPSON: Here is the
16 same thing in hardcopy. Sorry.
17 It might be easier to read.

18 THE WITNESS: Yeah, so the
19 ones that you see here, are the
20 ones that I did look at.

21 BY MR. VAUGHN:

22 Q. Can you go ahead and read
23 those off for me, aloud?

24 A. Etminan, Panigrahy, Hecht,

1 Lagana, Madigan.

2 Q. And then at the top of that
3 it says with exhibits. What does that
4 mean? Does that mean like their CV and
5 their materials considered?

6 A. CVs, not thoroughly, but
7 just to get an idea of what their
8 background was and where -- what
9 institutions they were in.

10 And in reading the report,
11 if there was a material that I thought
12 was germane to what I was doing, that I
13 might have looked at those too.

14 Q. Did you consider the
15 experts' CV when you were critiquing
16 their opinions?

17 A. In terms of their background
18 or their institution they were in, or
19 what part of the CV?

20 Q. Any part of the CV?

21 A. No. No that was not apart
22 of my critique is what their CV would
23 have been.

24 Q. I'm not saying critiquing

1 their CV. I'm saying when you were
2 critiquing their opinions, did you
3 consider what their specialty and
4 background was?

5 A. I mean, yes, I would have
6 considered it. I don't think it played
7 any role in what my critique was though.

8 Q. Okay. Did you review the
9 literature that each plaintiff expert
10 relied on?

11 A. Not all.

12 Q. Approximately how much of it
13 did you review?

14 A. I think it might have
15 depended on who it was, but I relied
16 mostly on their report and not on the
17 materials that they used to derive their
18 report.

19 So 20 percent, if I felt it
20 was germane to what I was interested in.

21 Q. But you didn't consider all
22 of the citations that plaintiffs' experts
23 used to support their opinions?

24 MS. THOMPSON: Objection.

1 Form.

2 THE WITNESS: No, I did not.

3 BY MR. VAUGHN:

4 Q. Was there one expert report
5 that you focused on more than the others?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: No, not
9 really. I sort of gave them equal
10 weight and time relative to how
11 big they were and how detailed
12 they were.

13 BY MR. VAUGHN:

14 Q. Do you recall which one was
15 the largest expert report?

16 A. Not exactly. My best
17 recollection was Panigrahy, but I can't
18 swear to that.

19 Q. Do you recall approximately
20 how many pieces of literature
21 Dr. Panigrahy relied on?

22 A. I don't recall at all.

23 Q. So you don't know if it was
24 100, 200, 500 articles?

1 A. I do not.

2 Q. If you reviewed the article
3 that a plaintiffs expert relied on, would
4 that appear on your materials considered
5 list?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: If it was
9 included in the exhibits, which is
10 what this says is my reliance
11 document, then I would have had
12 it.

13 BY MR. VAUGHN:

14 Q. Well, if the exhibit just
15 gave the names of the studies and didn't
16 actually have the study itself there, did
17 you go and find that study to look at?

18 A. If there was a study I had
19 interest in, I wouldn't have had any
20 assessment on it based on just reading
21 the title of the study. I would have
22 pulled the study if I felt like I needed
23 to look in.

24 Q. And then would that -- would

1 you have then included that on your
2 materials considered list in the area
3 that lists all the different studies that
4 you reviewed?

5 A. Not always.

6 Q. Why not?

7 A. If it ended up not being
8 something that was used to form my
9 opinions, then I didn't feel it was
10 relevant to put in my reliance list.

11 Q. And so you didn't even
12 critique the literature that plaintiffs'
13 experts relied on? It just wasn't
14 relevant to you?

15 MS. THOMPSON: Objection to
16 form. Mischaracterizes.

17 THE WITNESS: Yeah, I didn't
18 say it was irrelevant.

19 When I looked at them, I
20 would have decided if it was
21 relevant or irrelevant to what I
22 was doing.

23 BY MR. VAUGHN:

24 Q. Okay. How many deposition

1 transcripts with exhibits did you review
2 in forming your opinions?

3 A. The ones that are listed
4 here.

5 Q. And were each of those
6 transcripts several hundred pages?

7 A. Yes.

8 Q. Who is this Daniel Barreto?
9 I don't know if I'm saying the names
10 right.

11 A. I have to look at my notes.
12 He might have been a Teva employee.

13 Q. Do you know what any of
14 these depositions you reviewed -- can you
15 tell me who any of them are or who they
16 work for?

17 A. The one that I remember the
18 most because it -- was Nudelman. I know
19 he was a Teva employee involved in sort
20 of risk assessment or something like
21 that.

22 Q. Why did you -- why were
23 these the transcripts you decided to
24 review out of all the depositions that

1 have been taken in this litigation?

2 A. These were the ones that I
3 received from counsel.

4 Q. So counsel determined what
5 you reviewed?

6 MS. THOMPSON: Objection.

7 Form. Mischaracterizes.

8 THE WITNESS: No. Counsel
9 does not determine what I review.

10 BY MR. VAUGHN:

11 Q. Did you ask to review
12 certain depositions of people in certain
13 positions?

14 A. No.

15 MR. VAUGHN: All right. Can
16 we scroll down a little bit,
17 Tyler, on this regulatory guidance
18 and documents.

19 BY MR. VAUGHN:

20 Q. I note there's over 40
21 regulatory guidances and documents on
22 your materials considered. How did you
23 come into possession of all of these
24 regulatory guidelines?

1 A. Where are we now?

2 Q. Bottom of the page. So it
3 starts -- bottom of Page 1, and I think
4 it goes to -- two, three -- yeah, till
5 Page 3 is your regulatory guidance
6 documents.

7 A. I'd say some of them came
8 from counsel as part of what were called
9 my initial documents for consideration.
10 And some of them were documents that I
11 already had because in the nature of my
12 normal day-to-day job responsibilities,
13 as I try to keep track of what's going on
14 with the drugs that I have an interest
15 in.

16 So particularly, the FDA
17 documents, most of those I had already.

18 Q. So you reviewed all these
19 guidance documents, correct?

20 A. Yes.

21 Q. Did you have -- did you have
22 any disagreements with any of these
23 guidance documents?

24 A. I mean, how many did you say

1 there were?

2 Q. About 40.

3 A. Yeah, I can't recall
4 specifically if I would have had an
5 agreement within one or, you know, out of
6 all the things it would have been in all
7 the -- each of the individual 40
8 documents. So I don't recall that
9 specifically.

10 Q. If you disagreed with the
11 regulatory guideline, would that be not
12 significant?

13 MS. THOMPSON: Object to
14 form.

15 THE WITNESS: I don't know
16 what significant would mean.

17 BY MR. VAUGHN:

18 Q. I mean, would you not note
19 it in your expert report if you disagreed
20 with one of the regulatory guidance
21 documents?

22 A. Only, I suspect -- because I
23 don't recall doing it. But only if I
24 suspect it would have altered one of my

1 opinions.

2 Q. Do you know if any of these
3 regulatory guidance documents lay out the
4 methodology in which you -- and how you
5 convert animal exposure to NDMA to human
6 exposure?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: There may have
10 been areas that touched on that in
11 some of these documents. But I
12 don't recall specifically which
13 ones and where.

14 BY MR. VAUGHN:

15 Q. Would you agree that would
16 be important for your methodology to
17 follow what is laid out in the regulatory
18 guidelines?

19 MS. THOMPSON: Objection.

20 Form.

21 THE WITNESS: In terms of
22 forming my opinion on the
23 distribution and metabolism of
24 NDMA and NDEA?

1 BY MR. VAUGHN:

2 Q. On the equivalent dose for a
3 human based on what an animal got.

4 A. Well, that question
5 specifically has been addressed, not just
6 in regulatory documents, but in many,
7 many, many of the articles that I
8 reviewed in the animal studies.

9 And I don't recall ever
10 seeing a single one that did not list
11 that as a limitation in expanding animal
12 data to humans in this regard.

13 Q. Did you give more weight to
14 an article or to a regulatory guidance?

15 A. I guess I don't look at it
16 in those terms, to say one is better than
17 the other or stronger than the other.

18 I would say that in general,
19 regulatory documents look at a variety of
20 clinical and/or animal situation or data
21 as opposed to one single study.

22 So in a pure volume
23 standpoint, there would probably be more
24 data reviewed in a regulatory document.

1 But that's not always the case.

2 Q. If the regulatory document
3 laid out a different methodology than
4 some random study, which would you use?

5 MS. THOMPSON: Objection.
6 Form.

7 THE WITNESS: Which would I
8 use to do what with?

9 BY MR. VAUGHN:

10 Q. To convert the dose of NDMA
11 given to an animal, to the equivalent
12 dose needed to give a human.

13 A. Well, again, I'm not sure
14 exactly what you're asking. So maybe you
15 can rephrase it, and I'll try to do a
16 better job of answering.

17 Q. No. It was a bad question.
18 You're okay. We'll get to it here in a
19 little bit.

20 A. Okay.

21 Q. Did you conduct your own
22 literature review in forming your
23 opinions?

24 A. Yes.

1 Q. Can you explain your
2 methodology on your literature review to
3 me?

4 A. Yeah. I'd be happy to.
5 Original communications
6 between counsel and myself, I was asked
7 to evaluate the metabolism and
8 distribution of NDMA and NDEA. And then
9 with a focus of -- in regards to the
10 amount that had been identified in the
11 valsartan tablets.

12 And so after my original
13 review of documents that were provided in
14 those initial files, one of those was
15 also the pleadings from plaintiffs.

16 And even before I did my
17 literature search, I went through those
18 and tried to identify areas that were
19 within my area of expertise, like
20 bioequivalence, drug metabolism, and
21 those types of things. So I sort of knew
22 what direction I was wanting to head.

23 And then I went to PubMed
24 and started looking at articles relative

1 to NDMA and NDEA and metabolism,
2 dose-response, drug distribution.

3 And then, in addition, I
4 looked at valsartan as well, just because
5 there seemed to be issues about whether
6 there was potential overlapping
7 metabolism between valsartan and the
8 impurity.

9 So I included valsartan,
10 which pretty well characterized it, so it
11 didn't take too long anything that I
12 needed to find out about valsartan.

13 MR. VAUGHN: Tyler, can we
14 go to the next page of this
15 reliance list, or materials
16 considered. One more page.
17 Sorry.

18 BY MR. VAUGHN:

19 Q. At the bottom -- yeah, so
20 literature and standards down here. I
21 note that you have approximately 100,
22 117 pieces of literature on here. Were
23 you saying earlier that there's even more
24 literature than this that you reviewed,

1 you just didn't include it on your
2 materials considered?

3 A. Yeah. I think there's more.
4 Sometimes I would look at an article that
5 I thought was relevant. And then one of
6 my additional things that I do, instead
7 of just relying on my PubMed returns, is
8 I look at the references that are in that
9 article.

10 And sometimes you find one
11 that you might not have found through a
12 PubMed search. And I decide whether that
13 adds additional information or is
14 supportive or -- so, yeah, there's other
15 articles beyond these that, in the course
16 of the last four or five months, that I
17 looked at as well.

18 Q. I mean, if you had to
19 estimate, how many more? Like twice as
20 many, another dozen?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: I really can't
24 give you a number. It could be

1 between 25 and 75. I don't really
2 recall.

3 BY MR. VAUGHN:

4 Q. So less than 200 articles in
5 total you reviewed then?

6 A. Maybe. It could be more
7 than that.

8 Q. So you reviewed five expert
9 reports with the exhibits, eight
10 deposition transcripts with exhibits,
11 over 40 regulatory documents, and
12 approximately 200 pieces of literature
13 and 100 or so internal documents, and you
14 did all of that in 100 to 120 hours; is
15 that correct?

16 A. That is correct.

17 Q. Doctor, is this litigation
18 the first time that you ever researched
19 the carcinogenicity and potency of a
20 probable human carcinogen?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: Probably the
24 first time to this level of

1 research. But the concepts here
2 are essentially the same for any
3 new drug or any grant that I
4 submitted, where you have to be
5 thorough in your approach to
6 evaluating the literature,
7 selecting that, that you think is
8 relevant to what your question is
9 that you're trying to answer.

10 And so I -- it's maybe the
11 second time that I've looked at
12 what would be a potential
13 carcinogenic response to a drug.
14 But it's not any different from
15 what I've done for the last
16 35 years.

17 BY MR. VAUGHN:

18 Q. I know you don't believe
19 NDMA or NDEA to be human carcinogens.
20 But would you agree with me that they are
21 animal carcinogens?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: Yes. There

1 are numerous, numerous studies
2 showing carcinogenicity in
3 animals.

4 BY MR. VAUGHN:

5 Q. Are you aware of any animal
6 that NDMA is not a carcinogen in?

7 A. I didn't approach it looking
8 for one that escaped that. So I don't
9 know. I'm not aware of any, I don't
10 know.

11 Q. So you didn't consider if
12 every mammal ever tested with NDMA was
13 found to -- scratch that. Let me re-ask
14 the question.

15 So you didn't consider if
16 every animal is susceptible to cancer
17 formation when exposed to NDMA?

18 A. There's no opinion in my
19 report that was based on that, so no.

20 Q. Is a human an animal?

21 A. Yes.

22 Q. I'm sorry. For the jury.

23 So if every animal -- ever
24 mammal tested with NDMA was found to

1 increase their risk of cancer, would that
2 not be relevant to your opinion on if
3 NDMA is a human carcinogen also?

4 MS. THOMPSON: Objection.
5 Form.

6 THE WITNESS: No. And
7 again, I don't differ from the --
8 from the IARC's designation that
9 this is a probable human
10 carcinogen. I don't disagree with
11 that assessment.

12 And as I said before, with
13 the availability and the
14 limitations of the epidemiology
15 studies that have been done, those
16 were available to IARC and they
17 still didn't change that
18 designation from probable.

19 So the number of animal
20 species that had cancer responses
21 to various, and I might add super
22 high doses relative to what we are
23 talking about with NDMA, that
24 didn't change anything for me.

1 BY MR. VAUGHN:

2 Q. So at least in regards to
3 animals, NDMA and NDEA are the most
4 potent carcinogens that you've ever
5 investigated, correct?

6 MS. THOMPSON: Objection.
7 Form.

8 THE WITNESS: I mean,
9 possibly, yes.

10 MR. VAUGHN: Tyler, can we
11 go to Exhibit A of his expert
12 report now.

13 I think this will be
14 Exhibit 3 Tyler.

15 TRIAL TECH: Exhibit 3.
16 Yes.

17 (Document marked for
18 identification as Exhibit
19 Bottorff-3.)

20 MR. VAUGHN: Thank you. Can
21 we go to Page 11 of the PDF.
22 Perfect.

23 BY MR. VAUGHN:

24 Q. Doctor. It looks like

1 you've been involved in many journals.
2 What does it mean to be an editor of a
3 journal?

4 A. When researchers write
5 articles to be considered for
6 publication, they first go to an editor.
7 And the editor makes a preliminary
8 decision about whether it's worthy or not
9 of publication.

10 And if they believe it is
11 and within the scope of what that journal
12 focuses on, then they will send it out to
13 individual reviewers to provide specific
14 comments on all of the methodology and
15 conclusions and statistics and so forth.

16 So the editor level is sort
17 of one step above the individual journal
18 article referees or reviewers.

19 Q. How do you become either a
20 referee or an editor on a journal?

21 A. Usually those journals will
22 call me. Often it's a journal that I've
23 published in several times already. And
24 based on your expertise and experience,

1 they will invite you to be an editor. So
2 it's a selection, not something that you
3 volunteer for.

4 Q. So being an editor on a
5 journal is kind of a way of -- you've
6 been recognized as one of the leaders in
7 that area. Is that fair to say?

8 A. Very fair to say, correct.

9 Q. Have you ever worked --
10 sorry.

11 Have you ever been an editor
12 or reviewer or referee for a journal that
13 has a focus on cancer?

14 A. No. My focus has been
15 cardiovascular drugs, but again,
16 everything within the realm of those
17 drugs involving their pharmacology,
18 pharmacokinetics, pharmacodynamics,
19 safety, efficacy.

20 Q. So, you know, sometimes
21 people publish in journals that's a
22 little outside of the scope of what their
23 article is on. Have you ever been
24 involved in the peer review process of an

1 article on cancer, that was submitted for
2 publication?

3 A. Gosh, you know, some of
4 these were 25 to 30 years ago, so I don't
5 recall. I know it wouldn't have been a
6 major area of the articles that I would
7 have been asked to review. But it's
8 possible there was something there. And
9 I didn't -- that I just don't recall.

10 MR. VAUGHN: Tyler, can we
11 go to Page 3 of this document, PDF
12 Page 3.

13 BY MR. VAUGHN:

14 Q. I see there's like 141
15 invited presentations that you listed.

16 A. Is that all?

17 Q. Right. Can you explain to
18 me what invited presentations are?

19 A. Anywhere from -- yeah,
20 because those are followed by scientific
21 presentations. So I've done about maybe
22 1,500 internationally and nationally.

23 I break them down into two
24 types. One would be if a professional

1 society, a local organization, a
2 pharmacist, physicians, nurses would ask
3 me to give a presentation, that would be
4 an invited presentation in that setting.

5 The other ones that are more
6 scientific are typically either
7 professional societies or places like
8 hospitals to do grand rounds and those
9 types of things.

10 Q. Of all these invited
11 presentations, of the 141 listed, do any
12 of them relate to the carcinogenicity of
13 a substance?

14 MS. THOMPSON: Object to
15 form.

16 THE WITNESS: No, they all
17 relate to the safety, efficacy,
18 therapeutic decisionmaking, if you
19 will, of cardiovascular drugs in
20 general.

21 BY MR. VAUGHN:

22 Q. You're noting the different
23 types of people -- or organizations that
24 would invite you to give these

1 presentations. Would any of them be
2 pharmaceutical companies?

3 A. No, I wouldn't have listed
4 those. And they usually don't invite
5 someone like me to just come in and give
6 a presentation. I have done, in
7 40 years, maybe three or four of those.
8 But that's not a usual thing that
9 happens.

10 Q. Have you ever given a
11 presentation on behalf of a
12 pharmaceutical company?

13 A. Yes. And that gets back to
14 the speaker bureau question that we had
15 earlier this morning.

16 Q. And they pay you for those
17 presentations?

18 A. Correct. And these
19 professionals societies, when they invite
20 you, they pay you as well.

21 Q. But, again, some of the
22 presentations that you've given, you were
23 hired by a pharmaceutical company, but
24 you weren't presenting to the

1 pharmaceutical company, correct?

2 A. Correct. I was presenting
3 to other healthcare professionals.

4 Q. Do you disclose to them when
5 you are presenting, that you're hired to
6 present to them by the pharmaceutical
7 company?

8 A. Yes. That's required.

9 Q. And then under the
10 scientific presentations that you were
11 also talking about, do any of them relate
12 to the carcinogenicity of a substance?

13 A. No. I don't believe so.
14 They're all related again to the complete
15 profile and safety and efficacy and the
16 therapeutic application of any
17 cardiovascular drug that I had an
18 interest in.

19 MR. VAUGHN: Tyler, can we
20 go to PDF Page 10.

21 BY MR. VAUGHN:

22 Q. You list numerous awards
23 spanning several decades. Do any of the
24 awards have anything to do with cancer

1 research?

2 A. No. I don't do cancer
3 research.

4 Q. Why don't you do cancer
5 research?

6 A. My focus is on
7 pharmacokinetics, pharmacodynamics, drug
8 metabolism, drug interactions with
9 cardiovascular drugs. And if cancer was
10 part of that, then that's part of that.
11 But --

12 Q. So in general, would you be
13 relying in your professional field on
14 someone who has a focus in cancer
15 research?

16 MS. THOMPSON: Objection.
17 Form.

18 THE WITNESS: Would I be
19 relying on -- I'm sorry. I'm not
20 sure I understand the question.

21 BY MR. VAUGHN:

22 Q. I guess -- so you said that
23 you don't really research carcinogenicity
24 of substances.

1 If you needed to know the
2 carcinogenicity of a substance in your
3 daily practice, where would you get that
4 information, would you defer -- would you
5 get it from an expert in the field?

6 MS. THOMPSON: Objection.
7 Form. Mischaracterizes.

8 THE WITNESS: Yeah, I'm not
9 sure under what circumstances that
10 might be. But yeah, I could --
11 oncology people were part of the
12 academic medical centers where I
13 was. So I could always have
14 access to them.

15 BY MR. VAUGHN:

16 Q. All right. You would agree
17 that the oncologists at the places that
18 you've worked at would be more qualified
19 to give an opinion on the carcinogenicity
20 of a substance than you?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: Not if it came
24 to the area of drug metabolism and

1 pharmacokinetics.

2 They would refer to me.

3 BY MR. VAUGHN:

4 Q. What about dose-response?

5 A. Pretty much the same thing
6 in the context of how a drug is
7 metabolized.

8 Q. Would you consult with them?

9 MS. THOMPSON: Objection.

10 Form.

11 THE WITNESS: If necessary.

12 MR. VAUGHN: All right. Can
13 we go to PDF Page 12 now, Tyler.

14 BY MR. VAUGHN:

15 Q. Again, you have lots of
16 committees that you've been on in your
17 career.

18 Do any of them, of these
19 committees, have a focus on cancer?

20 A. Again, I'm not trying to
21 recall every single committee that I've
22 been on, but I have been on, and chaired
23 institutional review boards where
24 cancer-related studies were part of the

1 submission. So I have interacted in
2 that -- in that regard.

3 Q. Do you recall any of those
4 cancer related studies that you just
5 referenced?

6 A. Not off the top of my head,
7 no.

8 Q. A long time ago?

9 A. I mean, in the range of 10
10 to 20 years ago, yes.

11 Q. Has the field of
12 pharmacology evolved in the last ten
13 years?

14 MS. THOMPSON: Objection.
15 Form.

16 THE WITNESS: Quite a bit.
17 BY MR. VAUGHN:

18 Q. What about cancer or our
19 knowledge on carcinogens?

20 A. It looks like it has, based
21 on some of the documents that I reviewed
22 for this.

23 MR. VAUGHN: And, Tyler, can
24 we go to PDF Page 14, please.

1 BY MR. VAUGHN:

2 Q. It looks like you have been
3 37 grants or contracts. What is a grant
4 or a contract?

5 A. A grant is typically
6 something you submit to a funding agency.
7 And they review and approve for funding.

8 A contract is more a
9 negotiation with a funding agency,
10 specifically for something that you want
11 to do. And you're not necessarily in
12 competition for other people like you
13 would be for a grant.

14 Q. Are you doing animal studies
15 here or just all different types of
16 studies?

17 A. Majority is human
18 pharmacokinetics, pharmacodynamics, and
19 drug interactions.

20 I have done animal studies.
21 I'm not sure I got funded for any of
22 those. But I have worked in a fair
23 number of animal studies.

24 Q. What experience do you have

1 with animal studies?

2 A. My earliest one is at the
3 University of Kentucky as a resident.
4 One of my projects was looking at drug
5 distribution based on obesity using a rat
6 model. These are called Zucker rats.

7 I was mostly just helping
8 out in the lab and looking at the
9 techniques. So I never became an author
10 on the paper. But I have done that in
11 animals.

12 I've also done a dog study
13 looking at isolated cardiac myocytes in
14 the lab. And I've done some did
15 defibrillation threshold studies in pigs,
16 which I do have publications on.

17 Q. Have you ever done any
18 carcinogenicity studies in animals?

19 A. No.

20 Q. In your opinion, what animal
21 or animals are most similar to a human in
22 how they are going to respond to a drug?

23 A. It depends. And -- you
24 know, when you're looking at a specific

1 drug metabolism, then what it appears --
2 and this popped up in many of the studies
3 that I looked at for my report -- that
4 the rat is actually the animal that seems
5 the most similar to humans for drug
6 metabolism based on a standardized weight
7 of the liver in the rat, versus the liver
8 of a human, and not quite so much so in
9 the other animal models of drug
10 metabolism.

11 Q. So are you telling our jury
12 that humans are more similar to rats than
13 they are to monkeys?

14 MS. THOMPSON: Objection to
15 form.

16 THE WITNESS: In terms of
17 opposing thumbs, I think we're
18 closer to monkeys. But in terms
19 of drug metabolism, sometimes
20 we're closer to rats.

21 BY MR. VAUGHN:

22 Q. What about our DNA? What
23 percentage of our DNA do we share with
24 monkeys? Do you know?

1 MS. THOMPSON: Objection.
2 Scope.

3 THE WITNESS: I think it's
4 probably in the 90 percent.
5 Something like that.

6 BY MR. VAUGHN:

7 Q. What percent of DNA do we
8 share with rats?

9 A. It's probably in the
10 88 percent. So it's not as far off as
11 you would think.

12 Q. But we're more similar, DNA,
13 at least wise, to a monkey than a rat,
14 correct?

15 MS. THOMPSON: Objection.
16 Form.

17 MR. VAUGHN: I appreciate if
18 you quit laughing, Counsel.

19 MS. THOMPSON: Sorry. This
20 is a really funny line of
21 questioning.

22 THE WITNESS: Again, I think
23 it depends on what you are talking
24 about. And for this litigation,

1 for the question that I was asked
2 to address, it just turns out that
3 drug metabolism of NDMA is more
4 closely related in the rat than it
5 would be in any of the other
6 species.

7 And that's not getting into
8 the oncology part of it. It's
9 just getting into the drug
10 metabolism part. And that's the
11 part where I focus.

12 BY MR. VAUGHN:

13 Q. Are there any oral human
14 studies of NDMA exposure?

15 A. Other than the epidemiology
16 ones that we've mentioned already?

17 Q. Mm-hmm.

18 A. I do believe there was a
19 ranitidine study that looked at urinary
20 NDMA. I didn't focus on it for this
21 particular question that I was asked to
22 address. But I think there is at least
23 one that I can vaguely recall seeing.

24 Q. And did it look into the

1 metabolism of NDMA in the human body?

2 A. Not that I recall. But
3 again I didn't -- it's been a while since
4 I saw that one. So I haven't considered
5 it recently.

6 Q. What are you basing your
7 opinion on that humans metabolize NDMA
8 the same -- most similarly to rats of any
9 animal?

10 A. Numerous mentions of that in
11 the articles that I considered for this.
12 And I'm trying to recall. I probably
13 have in my note when it happened. If we
14 want to take the time to do that, I can
15 recall one specifically.

16 But my recollection is I saw
17 that as many as four or five times
18 mentioned.

19 Q. Did you look to see how they
20 came to their opinion on that?

21 A. Again, in the absence of
22 pharmacokinetic studies in humans, it was
23 more based on either rat 2E1, which is
24 the major metabolizing enzyme in question

1 here for NDMA, and NDEA for that matter.
2 That was one area that was discussed.

3 And then another area was
4 the volume that you can isolate of P450
5 per gram of liver in the rat is similar
6 if not close to identical to what you see
7 with that same calculation in the human.

8 Q. Is P450 an important --
9 strike that question.

10 What organs in the human
11 body have P450?

12 A. Many. But in almost every
13 study that I've ever seen, the majority,
14 by an overwhelming majority is the liver.
15 You do have, depending on the enzyme,
16 some in the gut wall, like the upper
17 small intestine, the kidney, the lungs.

18 There are a variety of other
19 organs that have been identified to have
20 it. But on a rank order, it's liver far
21 and away number one, gut wall number two.

22 Q. And so would you agree with
23 me that an organ or tissue must contain
24 P450 in order for NDMA to be able to

1 incite cancer in that organ?

2 A. Yes. And that's been
3 written about in numerous of the studies
4 that I reviewed.

5 Q. And so you would also agree
6 that organs with P450, if exposed to
7 NDMA, could be susceptible to cancer
8 formation?

9 A. Depending on the dose. And
10 then depending on the amount of P450 in
11 that organ, because they don't all have
12 the same amount.

13 So if you give the same dose
14 to two different organs and have one
15 organ that has ten times the P450 of the
16 other, and then it would produce a
17 different amount of carcinogen at that
18 point.

19 So it is relying on both the
20 dose, the amount of P450, and technically
21 in the way in which the drug is
22 administered as well.

23 Q. But you're unable to tell me
24 how much of a dose of NDMA is needed in a

1 human, right?

2 MS. THOMPSON: Object to
3 form.

4 THE WITNESS: No one has
5 that data.

6 Sorry.

7 BY MR. VAUGHN:

8 Q. These grants and contracts
9 that you received, are any of them from
10 pharmaceutical manufacturers?

11 A. Some of them are. Yes.

12 Q. What's the most recent grant
13 or contract that you received, do you
14 recall, or do you know?

15 A. I can tell you looking here.
16 2013, which is around the
17 time that I started switching my
18 responsibilities from primarily a
19 researcher clinician, educator, faculty
20 member to picking up more administrative
21 responsibilities.

22 Q. You are no longer conducting
23 research, correct?

24 MS. THOMPSON: Objection.

1 Form.

2 THE WITNESS: Not in the way
3 in which would be reflected in
4 terms of doing, you know, a grant
5 submission or something like that.

6 But again, you know,
7 researching drugs, their
8 pharmacology, that's almost a
9 daily thing for me for 40 years.

10 MR. VAUGHN: And, Tyler, if
11 we can go to PDF Page 15.

12 BY MR. VAUGHN:

13 Q. So your publications start
14 there. And it looks like you have about
15 50 publications listed. Do any of your
16 publications focus on cancer?

17 A. No, none of my publications
18 focused on cancer. But you can see that
19 they are heavily involved in drug
20 metabolism, drug pharmacokinetics, drug
21 pharmacodynamics.

22 MR. VAUGHN: And, Tyler, can
23 you go to 19.

24

1 BY MR. VAUGHN:

2 Q. At the bottom you list
3 original research. What do you mean by
4 original research?

5 A. I try to break down
6 publications by either books or book
7 chapters that I've authored compared to
8 review articles, you know, which are sort
9 of an overview of a particular drug or
10 drug topic.

11 But then original research
12 are the actual studies that I conducted,
13 most of the time in collaboration with
14 others, and then have those published.

15 Q. And of your original
16 research, any of it relate to cancer?

17 A. No. Again, it's all on
18 pretty much a drug pharmacokinetics, drug
19 metabolism, drug interactions, and
20 pharmacodynamics.

21 Q. All right. So, Doctor, I
22 don't see anywhere within your CV
23 anything on cancer.

24 Can you explain to our jury

1 why you believe that you are qualified to
2 provide an opinion as to the potency of a
3 carcinogen?

4 MS. THOMPSON: Objection.
5 Form.

6 THE WITNESS: Again, I don't
7 think that I'm claiming anything
8 involving potency in the way in
9 which I think of that term from a
10 pharmacodynamic standpoint.

11 But again, the question that
12 I was asked to review was how was
13 NDMA and NDEA metabolized and
14 where would they go and what would
15 happened to them at these doses.

16 And, you know, without
17 sounding flippant, metabolism of
18 compounds evolved long before we
19 put drugs in capsules and tablets.

20 So whether the chemical is
21 NDMA and is going through
22 cytochrome P450, whether it's a
23 cardiovascular drug or
24 noncardiovascular drug, it's going

1 through cytochrome P450.

2 Those principles are
3 identical, and in fact were
4 originally for ingested compounds,
5 long before we made capsules and
6 tablets.

7 So P450 has been around for
8 way longer than valsartan for
9 instance.

10 BY MR. VAUGHN:

11 Q. What is your definition of
12 potency?

13 A. Potency would typically be a
14 dose-response curve where you give
15 multiple doses and then characterize the
16 dose-response curve of two different
17 substances. And if there is a shift to
18 the left or to the right, then one of
19 those would be considered more potent
20 than the other.

21 That's how potency is
22 defined in drug pharmacology.

23 Q. As a pharmacist, do you
24 think you are more qualified than a

1 cancer research specialist to opine on
2 the potency of a carcinogen?

3 MS. KAPKE: Object to form.

4 MS. THOMPSON: Objection.

5 Form.

6 THE WITNESS: As a
7 pharmacist, what I'm probably more
8 qualified than anyone that I've
9 read depositions or expert reports
10 on, is to comment on drug
11 metabolism and drug distribution,
12 and a dose-response relationship
13 to that pharmacokinetic
14 distribution.

15 BY MR. VAUGHN:

16 Q. When that substance is a
17 potential carcinogen, you still think
18 that you're more qualified than a cancer
19 research specialist?

20 MS. THOMPSON: Objection.

21 Form.

22 THE WITNESS: In the context
23 of what I focused on about drug
24 metabolism, absolutely.

1 BY MR. VAUGHN:

2 Q. Did you do research to see
3 if, you know, any of the properties of
4 NDMA would change the way it's
5 metabolized in comparison to a
6 pharmaceutical drug?

7 MS. THOMPSON: Objection.
8 Form.

9 THE WITNESS: Yes, I did
10 actually.

11 And again, many of my
12 research and publications has
13 centered on not just drug
14 metabolism, but routes of drug
15 metabolism as a way of predicting
16 drug interactions.

17 And the number one cause of
18 a drug interaction is having two
19 co-administered compounds that
20 compete for the same metabolic
21 pathway.

22 And so one of my areas of
23 review was to describe how
24 valsartan is distributed and

1 metabolized, eliminated. And the
2 same for NDMA and NDEA. And I
3 think clearly demonstrated in my
4 report, that there's no overlap at
5 all, so there would be no
6 expectation of any -- having any
7 effect on each other because of
8 not sharing routes of elimination.

9 BY MR. VAUGHN:

10 Q. When you were determining
11 the levels that were -- of NDMA that were
12 given to animals, and you were trying to
13 opine what level would be needed for a
14 human to be equivalent, did you base that
15 in part off of the weight of the human?

16 MS. THOMPSON: Objection.
17 Form.

18 THE WITNESS: I mean, we can
19 look at that section in my report.
20 But the way in which I tried to
21 do, with all its limitations, the
22 extrapolation of the animal data,
23 particularly rats, because I think
24 they are the closest approximation

1 to humans, into human dose
2 equivalence, then that was done on
3 a milligram-per-kilogram basis.

4 So yes, it incorporated the
5 weight differential between the
6 two species, if you will, humans
7 and animals.

8 BY MR. VAUGHN:

9 Q. As a pharmacist and, you
10 know, the medications that you deal with,
11 is that how you convert every medication?
12 You do it the same way?

13 A. Convert from what to what?

14 MS. KAPKE: Object to form.

15 BY MR. VAUGHN:

16 Q. From an animal to a human?

17 A. Sometimes. I think it
18 depends on what's been done. And
19 sometimes they use body surface area.
20 But the usual way it's done is on a
21 milligram-per-kilogram basis.

22 Q. Usual way, but not always,
23 right?

24 A. Usual way but not always.

1 Q. Is there any -- is there any
2 medication you're aware of or substance
3 where scaling for weight is
4 inappropriate?

5 MS. THOMPSON: Objection.
6 Form.

7 THE WITNESS: Off the top of
8 my head, I can't say. I suspect
9 that it could be there. But I
10 can't say. I don't know off the
11 top of my head.

12 BY MR. VAUGHN:

13 Q. What factors would make it
14 inappropriate to scale based on weight?

15 MS. THOMPSON: Objection.
16 Form.

17 THE WITNESS: Well, not
18 having seen that done very much, I
19 don't have -- I don't have an
20 opinion on what that would be.

21 BY MR. VAUGHN:

22 Q. And so you didn't consider
23 what factors might make scaling for
24 weight when converting NDMA from an

1 animal to a human, you didn't consider
2 what factors might make that
3 inappropriate?

4 A. If I had ever seen in the
5 articles that I did review any allusion
6 to that, then I would have considered it.
7 But I didn't see it anywhere.

8 Q. You didn't see it anywhere.
9 But you would have considered though if
10 you did see it?

11 A. I would have always
12 considered it if I saw it.

13 Q. And would it have been in
14 your report then if you saw that?

15 A. Yes.

16 MR. VAUGHN: Counsel, right
17 now is another really good time
18 for a break. I know we're about
19 an hour.

20 (Whereupon a discussion was
21 held off the record.)

22 THE VIDEOGRAPHER: The time
23 right now is 11:11 a.m. We are
24 off the record.

1 (Short break.)

2 THE VIDEOGRAPHER: The time
3 right now is 11:26 a.m. We're
4 back on the record.

5 MR. VAUGHN: All right.
6 Tyler, can you pull the expert
7 report back up for us. And let's
8 go to Page 63 again.

9 BY MR. VAUGHN:

10 Q. Doctor, can you read that
11 opinion of yours at the bottom, VIII?

12 A. Yes.

13 "It is my opinion that no
14 scientific professional could credibly
15 claim to a reasonable degree of
16 scientific certainty that plaintiffs'
17 cancer was caused by their treatment with
18 any valsartan product contain trace
19 levels of NDMA and NDEA impurities during
20 the time period in question."

21 Q. Doctor, what do you consider
22 trace levels?

23 A. The amounts that I consider
24 to be trace in these valsartan products.

1 Q. And that was 20 micrograms
2 or less, correct?

3 A. Correct.

4 Q. And you say any valsartan
5 product. How could you give that opinion
6 when you haven't even reviewed all of the
7 testing data?

8 MS. THOMPSON: Objection.
9 Form.

10 THE WITNESS: Any valsartan
11 product that I evaluated.

12 BY MR. VAUGHN:

13 Q. Okay. So again, just less
14 than the 20 micrograms is what your
15 opinion is limited to?

16 MS. THOMPSON: Objection.
17 Form.

18 THE WITNESS: Not really.

19 BY MR. VAUGHN:

20 Q. So would it be more accurate
21 to say that any valsartan product that
22 the FDA reviewed?

23 MS. THOMPSON: Objection.
24 Form.

1 THE WITNESS: No. What I
2 used to draw that conclusion in my
3 report were the levels of exposure
4 to NDMA and NDEA in the animal
5 studies that provided
6 dose-response relationships that
7 appeared to confine, number one,
8 doses of NDMA that would not leave
9 the liver due to first-pass
10 metabolism, and that also did not
11 appear to cause cancer in
12 predominately rats because they're
13 the best model for this.

14 BY MR. VAUGHN:

15 Q. You're aware -- if you were
16 aware that the NDMA or NDEA levels in
17 generic valsartan were higher than what
18 the FDA was aware of, is that something
19 that you would have considered in forming
20 your opinions?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: If we go back
24 to the ZHP, for instance, comment

1 that was earlier in my report of
2 120 parts per million.

3 BY MR. VAUGHN:

4 Q. Mm-hmm.

5 A. That would correspond to
6 only about twice as much as what the
7 highest amount was in any of the products
8 that I evaluated.

9 And if you look at my tables
10 on 35, 36, 37, 38, 39, we're still
11 talking about hundreds to thousands times
12 more that was shown to be safe in animals
13 than the amount even in that 120 parts
14 per billion -- or million that we talked
15 about.

16 Q. What if the levels were go
17 even higher than 120 parts per million?

18 A. I don't have that
19 information, so I don't know what that
20 would look like or how much that would
21 be. It's not enough information for me
22 to make an opinion on.

23 Q. Defense counsel would have
24 needed to provide that information to you

1 for you to provide an opinion on it,
2 right?

3 MS. THOMPSON: Objection.
4 Form.

5 THE WITNESS: Or the FDA or
6 anybody else.

7 BY MR. VAUGHN:

8 Q. So in this opinion, when you
9 say no scientific professional could
10 credibly claim, what do you mean by that?

11 Is that more than just
12 disagreeing with the other side. Are you
13 drawing into question their integrity in
14 making their opinions?

15 MS. THOMPSON: Objection.
16 Form.

17 THE WITNESS: No, I didn't
18 draw this conclusion based on
19 their opinions.

20 I drew that conclusion based
21 on my research into NDMA
22 metabolism and the dose-response
23 relationship that this seemed to
24 be far below that was associated

1 with any cancer in the hundreds to
2 thousands times lower.

3 BY MR. VAUGHN:

4 Q. Would you consider some of
5 the plaintiffs' experts to be scientific
6 professionals?

7 A. Within their field, yes.

8 Q. And did any of them make the
9 claim to a reasonable degree of
10 scientific certainty that a plaintiff's
11 cancer could have been caused by their
12 treatment with valsartan containing NDMA
13 or NDEA?

14 A. I believe they made those
15 claims. I'm not sure they had access to
16 the data that I've provided and whether
17 that would have changed their opinions or
18 not.

19 Q. And do you think that you
20 reviewed all of the data that they
21 reviewed?

22 A. Much of the same.

23 Q. And so this -- this opinion
24 is not directed to any specific

1 plaintiffs' expert?

2 A. No, it is not.

3 Q. And it's not directed at any
4 of them, correct?

5 A. Correct.

6 Q. Did you review
7 Dr. Panigrahy's CV? You said that you
8 did, correct?

9 A. I probably scanned it to
10 see, you know, what his background and
11 training was and what his interests were
12 and what his current position was.

13 Q. Can you tell our jury what
14 you recall about Dr. Panigrahy's
15 credentials?

16 A. The details of that, I don't
17 have off the top of my head. I'd have to
18 look at my materials.

19 Q. So you don't recall that
20 Dr. Panigrahy was a medical -- is -- was
21 a medical doctor and completed a surgical
22 residency?

23 A. If I looked at it I would
24 recall that.

1 Q. Do you recall if
2 Dr. Panigrahy has taught both surgery and
3 pathology at Harvard?

4 A. If that's what he did, I
5 would have recalled it if I saw it.

6 Q. All right. Do you recall
7 that Dr. Panigrahy has devoted almost his
8 entire career to studying cancer?

9 A. That rings a bell, yes.

10 Q. Do you recall that
11 Dr. Panigrahy has been an editor on
12 journals such as Carcinogenesis,
13 Neoplasia, Cancer Research, Clinical
14 Cancer Research and Nature Reviews
15 Cancer?

16 A. Not those details, I don't
17 recall.

18 Q. All the journals that I just
19 listed, they all deal with cancer,
20 correct?

21 A. I don't remember each one of
22 them. But I heard cancer a few times.
23 So I'm guessing that's the case.

24 Q. Does Carcinogenesis, does

1 that relate to cancer?

2 A. Yes.

3 Q. What about Neoplasia?

4 A. Yes.

5 Q. Cancer Research?

6 A. Yes.

7 Q. Clinical Cancer Research?

8 A. Yes.

9 Q. And Nature Reviews Cancer?

10 A. Yes.

11 Q. And previously you testified
12 that being an editor on a journal
13 signifies that you were a higher level or
14 respected individual in that field,
15 correct?

16 A. I think I --

17 MS. THOMPSON: Objection to
18 form.

19 THE WITNESS: Sorry.

20 I think I used the word
21 "recognized."

22 BY MR. VAUGHN:

23 Q. Okay. So would you agree
24 with me that Dr. Panigrahy -- or

1 Panigrahy is a recognized leader in the
2 field of cancer?

3 MS. THOMPSON: Objection.
4 Form.

5 THE WITNESS: He seems to
6 be.

7 BY MR. VAUGHN:

8 Q. Are you familiar with the
9 NIH?

10 A. Yes.

11 Q. Can you tell our jury what
12 the NIH is?

13 A. It's a research arm of the
14 federal government that conducts some of
15 its own research and then funds external
16 researchers who apply for grants.

17 Q. Have you ever received
18 funding from the National Institute of
19 Health?

20 A. I applied twice and did
21 not -- I got approved, but my priority
22 score wasn't high enough to receive the
23 dollars.

24 Q. So they just don't hand that

1 out to anybody, those grants, do they?

2 A. No.

3 Q. Are you aware -- are you
4 familiar with National Cancer Institute?

5 A. That's one of the branches
6 of the National Institutes of Health.

7 Q. That was going to be my next
8 question. Thank you.

9 And have ever received -- I
10 guess you have not received funding from
11 the National Cancer Institute either,
12 because that's part of the National
13 Institute of Health?

14 A. That's correct. I have
15 received no NIH funding of any of their
16 branches.

17 Q. Do you recall that
18 Dr. Panigrahy has received funding both
19 from the National Institute of Health and
20 the National Cancer Institute to study
21 cancer in -- on numerous occasions?

22 MS. THOMPSON: Object to
23 form.

24 THE WITNESS: I don't

1 recall -- sorry.

2 I don't recall those
3 details, but if they are in his
4 CV, I'm sure he did.

5 BY MR. VAUGHN:

6 Q. So you don't recall that the
7 first time that he received funding was
8 back in 1998 for advanced training in
9 surgical oncology with a focus in
10 laboratory research?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: I do not
14 recall that specifically.

15 BY MR. VAUGHN:

16 Q. And do you recall if the
17 National Institutes of Health and the
18 National Cancer Institute is still
19 funding Dr. Panigrahy to research cancer
20 to this very day?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: I do not
24 recall that detail.

1 BY MR. VAUGHN:

2 Q. Do you think the National
3 Institute of Health and the National
4 Cancer Institute would still be funding
5 Dr. Panigrahy's cancer research if they
6 questioned his credibility?

7 MS. THOMPSON: Objection.
8 Form.

9 THE WITNESS: They probably
10 would not fund someone whose
11 credibility that they questioned
12 based on the research that they
13 submitted for review.

14 BY MR. VAUGHN:

15 Q. Are you aware that
16 Dr. Panigrahy, one of the top cancer
17 researchers in the world, spent around
18 1,400 hours researching and drafting his
19 opinions in this case?

20 MS. THOMPSON: Objection.
21 Form.

22 THE WITNESS: I don't have
23 access to that information. So I
24 could not have been aware of that.

1 BY MR. VAUGHN:

2 Q. And you spent approximately
3 100 to 120 hours, right?

4 MS. THOMPSON: Objection.
5 Form.

6 THE WITNESS: So far, yes.

7 BY MR. VAUGHN:

8 Q. Would that be about
9 10 percent of the time that Dr. Panigrahy
10 spent?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: That's how
14 that would be calculated, yes.

15 BY MR. VAUGHN:

16 Q. Doctor, are you familiar
17 with the term bioavailability?

18 A. Yes.

19 Q. Can you explain to the jury
20 what bioavailability means?

21 A. Bioavailability is the
22 assessment of what percent of a drug
23 that's taken actually reaches what we
24 would call the systemic circulation,

1 which means you can measure it in the
2 bloodstream.

3 Q. When the substance is taken
4 orally, what primarily impacts the
5 substance's bioavailability?

6 A. Well, it's a multi-step
7 process. And so the first step in that
8 is the actual release of the compound
9 from, let's say the pill or tablet that
10 was taken. And there are a lot of
11 examples of pills that don't completely
12 release constituents.

13 But once they are, they are
14 typically absorbed in the small
15 intestine. And there is a round,
16 potentially, depending on the product, of
17 drug metabolism that occurs across the
18 small intestine.

19 And once absorbed there, it
20 goes directly into the liver where it
21 sees another round of potential
22 metabolism. And only after exceeding
23 those steps, would it then show up in the
24 bloodstream to measure its

1 bioavailability.

2 Then that would be expressed
3 as a percentage of the dose of that
4 particular drug or chemical that you
5 gave.

6 Q. Give me one -- I'm reading
7 the realtime. My internet cut out a
8 little bit, so I missed part of your
9 answer. So just give me one second.

10 You said that a lot of drugs
11 don't release their constituents. Can
12 you explain that further to me?

13 A. Yeah. It just depends on
14 the drug. It's been noted with a lot of
15 sustained-release drugs, for instance,
16 that they release the drug so slowly that
17 sometimes the product gets past the site
18 of absorption before all the drug in it
19 gets released. And, therefore, you don't
20 get as good as bioavailability as you
21 might expect you would get.

22 Q. Valsartan, would all of the
23 NDMA be released or would some of that
24 pass with the valsartan as it's being

1 excreted?

2 MS. THOMPSON: Objection to
3 form.

4 THE WITNESS: My suspicion
5 is that it would be released from
6 the dosage form, yes.

7 BY MR. VAUGHN:

8 Q. Your suspicion -- what do
9 you base your suspicion on?

10 A. Well, that dosage form is
11 the type that usually is pretty much
12 completely dissolved into its individual
13 components before or by the time it
14 reaches the upper part of the small
15 intestine.

16 Q. So this process that you've
17 been talking about of what impacts the
18 bioavailability of a drug that is orally
19 ingested, is that known as first-pass
20 metabolism?

21 A. Well, not necessarily. You
22 can give an injectable into the muscle
23 and measure bioavailability. And that
24 would not be going through first pass.

1 So first pass is more
2 pertinent to oral administration.

3 Q. That's what my question was,
4 is with oral administration, it's known
5 as first pass?

6 A. Yes.

7 Q. And the organs you said that
8 were primarily involved, which is
9 stomach, small intestine, liver?

10 A. Not so much the stomach.
11 Small intestine and liver.

12 Q. Okay. And you would never
13 expect to see NDMA in the blood of a
14 human, correct, because you believe that
15 the liver should be able to handle all of
16 it?

17 A. Well, let me -- let me
18 qualify that by saying that at the
19 amounts that were found in the -- of NDMA
20 and NDEA in the valsartan tablets, I
21 would not expect that to reach the
22 systemic circulation at all based upon
23 first-pass metabolism.

24 Q. If someone were to find it

1 in the blood, that means it got past the
2 liver, right?

3 A. I think that would be, if
4 the dose was high enough, possible.

5 Q. Well, regardless of the
6 dose, if it was found in the blood, that
7 means it got past the liver, right?

8 MS. THOMPSON: Objection.
9 Form.

10 THE WITNESS: Not
11 necessarily. It could have gotten
12 there from another source.

13 BY MR. VAUGHN:

14 Q. Such as?

15 A. There's known endogenous
16 production of NDMA. So that's possible.
17 It could have been an environmental
18 exposure that led to NDMA that you found.

19 Q. What about if someone orally
20 ingests NDMA, and after orally ingesting
21 it, the levels of NDMA in their blood go
22 up?

23 MS. THOMPSON: Objection to
24 form.

1 THE WITNESS: Then that
2 would imply to me that the dose is
3 far exceeding the doses that we
4 are talking about here.

5 BY MR. VAUGHN:

6 Q. Sorry. My internet is
7 really bad here. You said that would
8 imply to you that the dose is far
9 exceeding the doses that we were talking
10 about here.

11 Again, regardless of dose
12 though, you could -- if you saw that,
13 it's getting past the liver, correct?

14 A. Yeah. But that wouldn't be
15 regardless of dose. It would be as a
16 result of the dose.

17 Q. And if we saw it in the
18 blood, that would mean that dose is
19 sufficient to get past the liver,
20 correct?

21 A. Correct.

22 Q. And would you also agree
23 then once it's in the blood, there are
24 many more organs in which the NDMA could

1 potentially impact?

2 A. There are multiple organs
3 that receive blood flow, if that were the
4 scenario, that would receive NDMA.

5 Q. And those tissues or organs
6 would be at risk for cancer formation,
7 correct?

8 A. Not necessarily.

9 Q. Why not?

10 A. Depends on the amount. It
11 depends on that organ's ability to remove
12 potential mutagens. And then it would
13 also depend on that organ's volume of the
14 specific enzyme that's involved in
15 creating the potential mutagen from NDMA.
16 And that specific P450 is called 2E1.
17 I'm sorry.

18 Q. No, I'm sorry. I didn't
19 mean to interrupt you.

20 A. It's all right.

21 And 2E1 has different
22 amounts in different organs. So there
23 are a lot of factors in play that would
24 have to be considered in that

1 hypothetical.

2 Q. You used the word "mutagen."
3 What is a mutagen?

4 A. A drug that alters DNA
5 structure.

6 Q. And is NDMA a mutagen?

7 A. Yes.

8 Q. And earlier I believe you
9 testified that human DNA is most similar
10 to a monkey's DNA, correct?

11 A. It most likely is. I
12 haven't looked at that information in a
13 long time.

14 Q. Of all the pharmaceutical
15 medications that you've worked with, how
16 many of them are also mutagens?

17 A. Gosh. I couldn't tell you
18 off the top of my head. Someone would
19 have had to have done a study
20 specifically looking for that.

21 Most of that work is done
22 when a drug is being developed in animal
23 studies before preclinical development,
24 and in most of those cases if there was

1 even a suspicion of that, it might not
2 have continued in the drug development
3 process. So I don't really have a good
4 number for you.

5 Q. Why would that -- why would
6 that be? Why, if there was a suspicion
7 that something was a mutagen, the drug
8 process would not continue?

9 A. Well, there's a variety of
10 reasons that a drug would be killed in
11 the preclinical process. In mutagenicity
12 studies, teratogenicity studies,
13 inability to get it stable in a dosage
14 form, a dependency on a specific P450
15 pathway that has a bunch of known drug
16 interactions.

17 I mean, the list is almost
18 endless. And the way that companies do
19 this, is they have maybe as many as 20 or
20 30 similar chemically related drug
21 candidates. And they do a variety of
22 those kind of studies on all those, and
23 what looks like the best to go forward
24 with are the ones that actually end up

1 making it in human trials.

2 Q. And so when a medication is
3 found to be a mutagen, it makes more
4 sense to kill the drug development
5 process than potentially kill a human,
6 right?

7 A. It depends on what the drug
8 is being developed for.

9 Q. And in which situation do
10 you think it would be okay to keep going
11 and give it to a human?

12 MS. KAPKE: Object to form.

13 MS. THOMPSON: Objection to
14 form.

15 THE WITNESS: I don't have a
16 lot of details of that part of the
17 drug development process.

18 So it also depends on what
19 disease it is they're trying to
20 treat and whether that's a risk
21 worth taking.

22 Those are -- those are
23 decisions made at the drug company
24 level looking at a variety of

1 factors.

2 BY MR. VAUGHN:

3 Q. Can you name a disease for
4 me that would be worse than cancer?

5 MS. THOMPSON: Objection.
6 Form.

7 THE WITNESS: I mean, there
8 are -- I don't know. There are
9 some that I'm sure somebody can
10 say is worse than cancer. It
11 depends on what type of cancer
12 we're talking about. So I don't
13 have a strong opinion on that at
14 all.

15 BY MR. VAUGHN:

16 Q. What type of cancer do you
17 think is the worst kind of cancer?

18 MS. KAPKE: Object to form.

19 MS. THOMPSON: Form.

20 THE WITNESS: The fatal
21 ones, I guess. I don't have a --

22 BY MR. VAUGHN:

23 Q. So can you name one drug
24 that you've worked with that is a

1 mutagen?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: What do you
5 mean by "worked with"?

6 BY MR. VAUGHN:

7 Q. Studied?

8 A. Did my own independent
9 research on? Or as part of my 40 years
10 of evaluating drugs and drug safety and
11 pharmacokinetics and drug metabolism, any
12 drug within that realm that could have
13 turned out to be a mutagen?

14 Q. Yeah, in any way. Can you
15 name drugs that you've worked with in
16 some way that are mutagens?

17 A. Actos, I think, is the one
18 that comes off the top of my head.

19 Q. What did Actos cause?

20 MS. THOMPSON: Objection.

21 Form.

22 THE WITNESS: I believe it
23 was bladder cancer.

24 BY MR. VAUGHN:

1 Q. And was the mechanism there
2 because it was a mutagen? Is that what
3 was resulting in the bladder cancer?

4 A. I assume so. I didn't get
5 into the details of the mechanisms of
6 mutagenicity or carcinogenicity. The
7 mechanisms of that are not what I do.

8 Q. Did you consider the
9 mechanisms of mutagenicity when forming
10 your opinions in this case?

11 A. Yes and no. I mean mostly
12 what I focused on was metabolism,
13 distribution, and drug dose-response.

14 Q. Do you know if mutagenicity
15 has any impact on drug dose-response?

16 MS. THOMPSON: Objection.
17 Form.

18 THE WITNESS: Well,
19 mutagenicity would be a drug dose
20 response, or could be.

21 BY MR. VAUGHN:

22 Q. Do you know if mutagenicity
23 has any impact on how you should be
24 scaling from an animal to a human?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: Well again, we
4 have all the limitations of
5 scaling from animals to humans.
6 And for me to form the opinions
7 that I did, I looked at the amount
8 of NDMA, NDEA in valsartan
9 products, the amounts that did not
10 seem to be carcinogenic, in what I
11 considered to be the best animal
12 model which is the rat model.

13 And so my opinions were
14 formed based on that relationship
15 between a drug dose that did not
16 appear to cause either -- at least
17 carcinogenicity, and in some cases
18 mutagenicity, and compared that to
19 the levels of valsartan-containing
20 products.

21 So did I consider
22 mutagenicity as part of my
23 evaluation? Yes, I did.

24 BY MR. VAUGHN:

1 Q. How --

2 A. In response to the drug or
3 chemical.

4 Q. How does mutagenicity impact
5 interspecies scaling, if at all?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: Well, I don't
9 think -- again, it's not the
10 mutagenicity that impacts the
11 interspecies scaling.

12 Interspecies scaling is
13 always going to be an
14 extrapolation that has its
15 limitations.

16 In every one of articles you
17 read, in at least the last
18 paragraph or two, it always says
19 we're unsure what it means in
20 humans.

21 And so we are unsure about
22 that. And so it's hard to say how
23 that impacts scaling because it's
24 not -- it's an inherent problem

1 with doing the scaling to begin
2 with.

3 BY MR. VAUGHN:

4 Q. Earlier, when we went
5 through your CV and the literature
6 review, you described to me the
7 methodology in which you found that
8 literature.

9 Did you seek out any
10 literature on if mutagenicity would
11 impact interspecies scaling?

12 A. I don't even know that
13 that's the question that I was looking
14 at.

15 What I can say is that some
16 of the dose-response studies,
17 particularly in rats by some of the
18 trials, studies in rats that I relied on,
19 they used mutagenicity as the
20 dose-response marker.

21 Q. Did you review any
22 literature on mutagenicity as it is
23 related to interspecies scaling?

24 MS. THOMPSON: Objection.

1 Form.

2 THE WITNESS: Again, I'm not
3 even sure what that question is.
4 So I have a hard time answering
5 it.

6 So I did say that I
7 considered mutagenicity in making
8 an opinion or forming an opinion
9 about dose-response relationships
10 with rats relative to the amount
11 of NDMA, NDEA that are found in
12 the valsartan products.

13 So I made those
14 extrapolations, understanding all
15 of the limitations quoted by
16 almost every author in the study
17 that I looked at.

18 BY MR. VAUGHN:

19 Q. Would you have scaled it the
20 same way regardless of if the substance
21 was a mutagen?

22 MS. THOMPSON: Objection.

23 Form.

24 BY MR. VAUGHN:

1 Q. Sorry, would you have scaled
2 from the animal studies with NDMA to
3 humans the same way regardless if the
4 substance was a mutagen?

5 MS. THOMPSON: Objection.
6 Form.

7 THE WITNESS: I mean, that's
8 just one of the dose responses
9 that you would -- that you would
10 try and extrapolate. So I'm not
11 even sure that I really understand
12 the question.

13 BY MR. VAUGHN:

14 Q. Okay. If NDMA was not a
15 mutagen, would your methodology have been
16 the exact same?

17 A. In terms of evaluating the
18 literature for drug distribution and
19 metabolism, yes.

20 Q. And dose-response and
21 interspecies scaling?

22 A. And it would have been a
23 different response.

24 Q. I want to focus on the

1 interspecies scaling.

2 A. Okay. What do you mean by
3 that?

4 Q. Okay. When you take it from
5 an animal -- let's say an animal weighs
6 one kilogram, okay?

7 A. Mm-hmm.

8 Q. And only one nanogram, let's
9 say, for that animal can cause cancer,
10 that 1 kg animal. How would you then --
11 using your methodology, how would you
12 determine how much would be needed to
13 give a human to cause cancer?

14 MS. THOMPSON: Objection to
15 form.

16 THE WITNESS: I didn't
17 evaluate it in those terms that
18 you're asking the question.

19 BY MR. VAUGHN:

20 Q. Explain to me again then how
21 you did your analysis on these animal
22 studies to come to these conclusions that
23 the valsartan contained so much more NDMA
24 than the animal studies?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: It's actually
4 the other way around.

5 The animal study doses, that
6 were often not related to any
7 cancer whatsoever, so mutagenicity
8 doesn't play a role in that
9 setting, I was able to find doses
10 that did not produce any mutagenic
11 or carcinogenic effect, and those
12 are the values that I used to make
13 my species extrapolation from --
14 from the rats to the humans.

15 So I was using the absence
16 of mutagenicity and
17 carcinogenicity, not the
18 production of it.

19 BY MR. VAUGHN:

20 Q. Are you saying most of the
21 animal studies regarding NDMA did not
22 cause cancer?

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: No. This gets
2 back to my whole premise and focus
3 in this review and report, is the
4 dose.

5 And obviously, and we talked
6 about this earlier this morning,
7 you know, if you give enough NDMA
8 and NDEA to many of the animal
9 species that we talked about, you
10 can induce cancer. And that's not
11 the question that I was
12 addressing.

13 I was addressing, is there a
14 dose below which it doesn't appear
15 to, and how does that relate to
16 what's in valsartan.

17 MR. VAUGHN: Tyler, can we
18 go back to his expert report.

19 Let's go to Page 21.

20 BY MR. VAUGHN:

21 Q. Under valsartan
22 pharmacokinetics, can you read the first
23 two sentences aloud for me?

24 A. "After oral administration

1 in humans, valsartan is absorbed into the
2 body primarily in the small intestine,
3 below the level of the stomach and
4 reaches peak plasma concentrations
5 between two and four hours.

6 "The amount of a given dose
7 that reaches the systemic circulation,
8 which means beyond the liver, is
9 expressed by the term of absolute
10 bioavailability and this ranges from 10
11 to 35 percent, averaging 25 percent."

12 Q. Is there any difference
13 between absolute bioavailability and
14 bioavailability, the terms?

15 A. Yes, in a way. They're just
16 adding a descriptor of absolute because
17 they have something when they did this
18 study to compare it to.

19 Let's say you gave a dose
20 of -- I don't know -- any drug and you
21 measured it in blood, then you can claim
22 that it has bioavailability. But what
23 you really have to do to calculate
24 absolute bioavailability is compare that

1 back to the intravenously given dose of
2 the same drug. And then the number that
3 you're calculating is absolute.

4 Q. And this absolute
5 bioavailability of valsartan is 10 to
6 35 percent. That's in humans, right?

7 A. Correct.

8 Q. Why is the bioavailability
9 of valsartan 350 percent higher in some
10 humans compared to others?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: Because of its
14 variability, do you mean?

15 BY MR. VAUGHN:

16 Q. Well, I mean, this range of
17 ten percent to 35 percent. 35 percent is
18 like 350 times higher than 10 percent,
19 right?

20 A. Yeah.

21 Q. Why is there such a wide
22 range on the bioavailability in humans?

23 A. For many drugs you would
24 find the same thing, so I don't consider

1 that to be abnormal at all. That's just
2 what drug variability is.

3 Q. That's expected, right,
4 there's going to be variability between
5 humans?

6 A. Yes. What we call
7 interindividual variability. But that
8 will be unique to whatever drug we happen
9 to be talking about.

10 Q. But typically there's
11 variability among humans, correct,
12 regardless of the substance?

13 A. There will always be some.
14 In some cases it's more than this, and in
15 some cases it's less than this in terms
16 of the variability.

17 Q. In terms of percent
18 bioavailability of valsartan, which
19 animal is the most similar to humans?

20 MS. THOMPSON: Objection.
21 Form.

22 THE WITNESS: I do not know.
23 Because we have human data, we
24 don't have to worry about it. And

1 so I don't know which model. I
2 assume if I were to go back and
3 look at the basic preclinical
4 studies, that probably someone in
5 Novartis or contracted by Novartis
6 did 25 to 30 years ago, that I
7 could probably find that. But --
8 and so I know it's out there. I
9 just haven't looked at it.

10 BY MR. VAUGHN:

11 Q. Do you agree that knowing a
12 medication's bioavailability is critical
13 in determining the dose necessary for a
14 specific outcome?

15 MS. THOMPSON: Objection to
16 form.

17 THE WITNESS: Well, the way
18 that question is asked, you know,
19 could go a lot of different
20 answers.

21 You know, if only 5 percent
22 of something is absorbed, but you
23 give a high enough dose to get the
24 effect, then it's the effect you

1 care about, and not whether it was
2 5 percent and whether you liked
3 the number 5 percent or not.

4 BY MR. VAUGHN:

5 Q. This 10 to 35 percent
6 bioavailability in your report, that's
7 specific to valsartan, right? That
8 doesn't have anything to do with the
9 bioavailability of NDMA or NDEA, correct?

10 A. Nothing to do with that at
11 all. They -- they're not attached to
12 each other. One doesn't carry the other.
13 So they're managed and handled
14 independently.

15 Q. Can you identify in your
16 report where you specified the
17 bioavailability of NDMA in humans?

18 A. I think in my report -- if
19 you give me a minute to look at it. Is
20 that all right?

21 Q. Absolutely. Take all the
22 time you need.

23 A. You're talking about NDMA or
24 NDEA?

1 Q. Yes, sir.

2 A. Yeah, I don't find where I
3 specifically listed a specific
4 bioavailability number. And the reason
5 probably for that is that it depends on
6 the dose because, unlike valsartan, this
7 is a highly subjective drug to first-pass
8 metabolism. And so as the dose goes up,
9 the bioavailability changes.

10 So it's not as fixed a
11 number as the valsartan bioavailability
12 would be.

13 Q. If there were studies in
14 which they were giving below -- scratch
15 that.

16 If there were studies in
17 which they were giving NDMA below what
18 would saturate the liver, would that
19 allow you to determine its
20 bioavailability?

21 A. Well, actually what you
22 would determine in that setting by
23 measuring something downstream from the
24 liver, you would measure zero, which

1 would mean it was essentially zero
2 bioavailability because it wouldn't get
3 into the systemic circulation, despite
4 being absorbed.

5 Q. So it's your opinion the
6 liver must be fully saturated before it
7 can get past the liver?

8 A. Absolutely.

9 Q. Is that with every animal?

10 A. That's with everybody with a
11 liver.

12 Q. And then -- so once it's
13 saturated, is every amount of the dose
14 going to be going past the liver?

15 A. Yes. Depends again on the
16 compound, the drug, and how else it might
17 be metabolized. But when it leaves the
18 liver, it goes into the venous
19 circulation.

20 Q. And so can you explain to me
21 again how you determine the
22 bioavailability of a substance?

23 A. The most pure way, if you
24 will -- excuse me -- is to give an oral

1 dose and an IV dose and compare how much
2 you measure in the bloodstream using
3 something called the area under the curve
4 or the AUC.

5 Q. And did you see any studies
6 like that on any animal?

7 A. I did.

8 Q. What animals?

9 A. Predominately rats. But a
10 few other species. I think I saw a
11 monkey study and a pig study and a dog
12 study. Actually two dog studies, maybe.

13 Q. And do you recall what the
14 bioavailability of NDMA is in rats?

15 A. It was less than 10 percent
16 at doses below, say, around .1 milligram
17 per kilogram given orally. So in the
18 range of 6 to 8 percent.

19 Q. What about monkey? Do you
20 recall what the bioavailability of NDMA
21 is in a monkey?

22 A. I think the study I saw was
23 it was higher. Maybe as much as 80 or
24 90 percent.

1 Q. 80 or 90 percent?

2 A. That's my recollection.

3 Q. So you're saying in monkeys,
4 80 to 90 percent of the NDMA you give
5 them is going to get past the liver?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: In the dose
9 that they gave in that monkey
10 study. That's going to get
11 back -- gets back to the heart of
12 what my whole premise here is, is
13 that bioavailability for a
14 high-clearance drug like NDMA is
15 based on the dose you give.

16 And I'm fairly certain in
17 the monkey study that it gave at
18 least a milligram per kilogram,
19 which is way above what I'm
20 contending is the liver's capacity
21 to completely metabolize NDMA and
22 spare downstream organs.

23 BY MR. VAUGHN:

24 Q. What about pigs? Do you

1 recall the bioavailability of NDMA in
2 pigs?

3 A. Yeah. I think that study
4 was around -- oh, I'm going to say
5 45 percent, something like that.

6 Q. And then do you recall the
7 bioavailability of NDMA in dogs?

8 A. I think it was somewhat
9 similar to the pigs. Maybe in that 40 to
10 50, 60 percent range.

11 Q. And so pigs, dogs, monkeys,
12 the bioavailability of NDMA is hundreds
13 of times higher than in rats, correct?

14 A. When you give a thousand
15 times higher dose, yes.

16 Q. But it's your opinion that
17 humans are most similar to rats in their
18 bioavailability of NDMA?

19 A. That is my contention. And
20 there's literature to support that.

21 Q. Is there literature that
22 goes against that?

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: Again, you
2 have to be very specific about the
3 doses given.

4 And the other animal species
5 that you're talking about, the
6 doses given were a thousand or
7 more times higher than the doses
8 that I'm talking about in the rat
9 studies that have been shown to be
10 completely metabolized in the
11 liver.

12 MR. VAUGHN: Give me just
13 one second.

14 THE WITNESS: And I should
15 add, while you're looking,
16 there's -- it's a little more
17 complicated than that.

18 When you look at these kinds
19 of bioavailability studies, not
20 only is the dose important to
21 determine what you're going to
22 call bioavailability, the two
23 other things that are important to
24 look at, one is interspecies

1 differences in the amount of the
2 cytochrome P450 enzyme that we're
3 talking about here, which is 2E1.

4 And so for a species to have
5 less than a rat, let's say, then
6 even the same dose would give a
7 higher bioavailability because
8 they have less metabolizing
9 capacity by having less 2E1. And
10 beagles, swine, and monkey
11 primates are all known to have
12 less 2E1 than rats.

13 So that factors into that
14 higher bioavailability.

15 And then to go even a little
16 bit deeper, and this gets into the
17 understanding of how you calculate
18 or use AUCs to calculate
19 bioavailability, is there's an
20 assumption that you make. And all
21 of these articles we're referring
22 to identify that assumption.

23 And they clearly identify in
24 their own self-criticism of their

1 study, is it makes the assumption
2 that when you give a drug IV, it's
3 metabolized nowhere but in the
4 liver because you're comparing the
5 oral dose that goes straight
6 through the liver with the IV
7 dose.

8 And the more there is
9 extrahepatic metabolism of the
10 drug, the more the overestimate is
11 of the bioavailability.

12 So using those
13 bioavailability numbers in animals
14 that have less 2E1 that made
15 invalid assumptions about the
16 calculations of bioavailability to
17 begin with, and then thirdly give
18 a thousandfold or higher dose than
19 what the liver can handle at
20 smaller doses, then I evaluated
21 those studies, but because I
22 didn't think they were germane to
23 the doses of NDMA that we're
24 talking about here, they didn't

1 alter my opinions in my report.

2 BY MR. VAUGHN:

3 Q. Part of the reasons those
4 doses were not -- or you do not consider
5 similar to the amounts given to humans is
6 because humans weigh more than those
7 animals, correct?

8 A. No. You can do it on a
9 milligram per kilogram.

10 The three other species
11 studies we're talking about, beagles,
12 pig, and monkey, some of them gave both 1
13 and 5-milligram-per-kilogram oral doses.
14 And if you do that on a scale of what's
15 in valsartan containing NDMA, we are
16 talking thousands and thousands times
17 higher doses.

18 And I think it might have
19 been the monkey study that only gave one
20 milligram per kilogram. They didn't do
21 the five as well.

22 So there are a lot -- there
23 are a lot of reasons why those trials did
24 not alter my conclusions, because they

1 weren't relevant to the doses that we are
2 talking about, and they weren't as close
3 a species for 2E1 metabolism.

4 Q. And you're saying humans are
5 more similar to rats than monkeys?

6 MS. THOMPSON: Objection to
7 form.

8 THE WITNESS: In 2E1
9 metabolism.

10 BY MR. VAUGHN:

11 Q. Doctor, we got through that
12 section a little quicker than I had
13 anticipated.

14 MR. VAUGHN: I think it's a
15 little after noon your guys' time.
16 If you want to take a lunch break
17 now, I think that would be --
18 that's okay with me.

19 MS. THOMPSON: That's fine
20 with me.

21 THE WITNESS: Yeah, that's
22 fine.

23 MR. VAUGHN: How long do you
24 guys want to take? We can go off

1 the record.

2 THE VIDEOGRAPHER: The time
3 now is 12:16 p.m. We're off the
4 record.

5 (Whereupon a luncheon recess
6 was taken.)

7 THE VIDEOGRAPHER: The time
8 right now is 1:07 p.m. We're back
9 on the record.

10 BY MR. VAUGHN:

11 Q. Doctor, you testified
12 earlier that NDMA is a probable human
13 carcinogen. Can you define for the jury
14 the word "probable"?

15 A. Again, I take that
16 definition from the IARC definition of a
17 known carcinogen in animals, but
18 insufficient data to call it a known
19 carcinogen in humans.

20 Q. Do you not have a definition
21 for the word "probable"?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: No, I don't.

1 BY MR. VAUGHN:

2 Q. Would you say that probable
3 is the same as more likely than not or a
4 higher level of proof?

5 MS. THOMPSON: Objection to
6 form.

7 THE WITNESS: Yeah, I don't
8 have an opinion on that.

9 BY MR. VAUGHN:

10 Q. Do you think probable is
11 possibly less than more likely than not?

12 MS. THOMPSON: Objection to
13 form.

14 THE WITNESS: I don't have
15 an opinion on that.

16 BY MR. VAUGHN:

17 Q. Does the bioavailability of
18 valsartan decrease as you decrease the
19 dose of valsartan?

20 MS. THOMPSON: Objection.
21 Form.

22 THE WITNESS: Not that I'm
23 aware of.

24 I don't recall seeing

1 anything in the -- in the
2 pharmacokinetic valsartan studies
3 that indicated that. So it's
4 probably of a similar amount
5 across its usual oral dosage
6 range.

7 BY MR. VAUGHN:

8 Q. Is that typical of most
9 drugs?

10 A. It depends. It depends on
11 their clearance and how they're
12 metabolized and what their dose range is.

13 Q. So why would valsartan --
14 because do you have to saturate it
15 before -- beforehand, the liver, before
16 it can get systemic?

17 MS. THOMPSON: Objection.
18 Form.

19 THE WITNESS: Well, unless
20 you're giving a drug orally with
21 the intent of treating the colon,
22 which is like what happens with
23 some drugs for ulcerative colitis
24 and Crohn's disease, then orally

1 administered drugs that are
2 supposed to have an effect
3 somewhere other than the colon or
4 the liver, then you have to give
5 it at a dose that will get to
6 those sites of action.

7 But I wouldn't characterize
8 the metabolism as having been
9 saturated at the doses that we
10 give for valsartan.

11 BY MR. VAUGHN:

12 Q. If valsartan is not
13 saturated in the liver then why is some
14 of the valsartan getting past the liver?

15 MS. THOMPSON: Objection.
16 Form.

17 THE WITNESS: In this case
18 it's a slowly metabolized drug.
19 So it just takes a while to
20 metabolize. So some drug is going
21 on into the bloodstream while the
22 other part that's still in the
23 liver is waiting to be
24 metabolized.

1 So, I mean, you could call
2 that a form of saturation if you
3 want. But it's -- it's not really
4 a form of saturation. It's a rate
5 of metabolism in this case.

6 BY MR. VAUGHN:

7 Q. And so I'm clear, the
8 valsartan does not have to saturate the
9 liver to get past the liver, correct?

10 MS. THOMPSON: Objection.
11 Form.

12 THE WITNESS: I don't
13 believe I've ever seen that
14 described as being a saturable
15 metabolism step.

16 BY MR. VAUGHN:

17 Q. Why with NDMA do you believe
18 that it must fully saturate the liver for
19 any amount of NDMA to get past the liver?

20 MS. THOMPSON: Objection.
21 Form.

22 THE WITNESS: Because its
23 rate of metabolism is different.
24 It's a faster rate.

1 BY MR. VAUGHN:

2 Q. What's the rate of
3 metabolism of NDMA?

4 A. I don't know that number off
5 the top of my head.

6 Q. What's the rate of
7 metabolism for valsartan?

8 A. I also don't know the number
9 off the top of my hand -- my head.

10 My point is that using the
11 term "saturation" to define what does or
12 does not get into the liver past the
13 bloodstream, it's more complicated than
14 that. It's based on rate of metabolism
15 and the amount given as well.

16 Q. How can you have the opinion
17 that NDMA is metabolized faster than
18 valsartan when you do not know the rate
19 of metabolism of either valsartan or
20 NDMA?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: Just its
24 clearance. Clearance.

1 BY MR. VAUGHN:

2 Q. Can you explain that a
3 little more?

4 A. Well, there's two types of
5 clearance. There's high clearance and
6 low clearance. And it depends on the
7 kind of drug and which one is going to be
8 more dependent on the intrinsic clearance
9 of the liver versus hepatic blood flow
10 itself.

11 And those ratios are all
12 different for different drugs.

13 Q. Are you aware of any
14 substances that can inhibit P450?

15 A. Yes. I'm aware of many.

16 Q. Can you list off the ones
17 that you're aware of?

18 A. Amiodarone, cimetidine,
19 azole antifungals, erythromycin,
20 clarithromycin, many of the HIV drugs.
21 The list goes on and on.

22 Q. So taking substances that
23 inhibit P450 increase the likelihood that
24 NDMA is going to get past the liver in a

1 human?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: Again, it
5 would depend on what the inhibitor
6 inhibits.

7 Some of these drugs I
8 mentioned only block P450-3A4 and
9 they don't touch 2E1, which is the
10 major P450 we're talking about
11 here. And in looking at my 2E1
12 metabolism, there are no listed
13 inhibitors for 2E1.

14 BY MR. VAUGHN:

15 Q. None?

16 A. None.

17 Q. What about alcohol?

18 A. Alcohol. You asked me about
19 drugs. And so I didn't list alcohol as a
20 drug.

21 Q. I apologize. So alcohol
22 could though?

23 A. Alcohol has been shown to
24 block 2E1.

1 Q. So it would be a bad idea to
2 be drinking alcohol if you were taking
3 valsartan contaminated with NDMA,
4 correct?

5 A. Actually, I should --

6 MS. THOMPSON: Objection to
7 form.

8 THE WITNESS: Sorry.

9 Let me clarify. I think
10 it's the alcohol that blocks 2A6
11 and not 2E1.

12 BY MR. VAUGHN:

13 Q. And what are you basing that
14 on?

15 A. The data.

16 Q. Are you aware of any other
17 substances -- doesn't have to be drugs --
18 any other substances that would inhibit
19 2E1?

20 A. I am not.

21 Q. What data are you relying on
22 to say that alcohol does not inhibit 2E1?

23 A. The fact that there isn't
24 any.

1 Q. So you're not aware of any?

2 A. I'm not aware of any.

3 Q. So you did not -- sorry.

4 A. I'm aware though of the
5 alcohol and the 2A6.

6 Q. If there is literature out
7 there on various substances that can
8 inhibit 2E1, you did not consider those
9 in forming your opinions in this case,
10 correct?

11 MS. THOMPSON: Objection.

12 THE WITNESS: I did not see
13 any.

14 Sorry.

15 MS. THOMPSON: You got to
16 let me object.

17 Objection to form.

18 Go ahead.

19 THE WITNESS: I did not see
20 any.

21 BY MR. VAUGHN:

22 Q. And so, therefore, you did
23 not consider it, correct?

24 A. Correct.

1 Q. Doctor, do you disagree with
2 the plaintiffs' experts that there is a
3 linear dose-response with NDMA or NDEA
4 and cancer with no dose threshold,
5 correct?

6 MS. KAPKE: Object to form.

7 MR. VAUGHN: Let me re-ask
8 that one.

9 BY MR. VAUGHN:

10 Q. Doctor, are you aware if
11 sedatives can impact 2E1 or inhibit 2E1?

12 MS. THOMPSON: Object to
13 form.

14 THE WITNESS: I don't recall
15 specifically seeing that. If I
16 did, my recollection was that it
17 was one of the older sedatives
18 that we don't use anymore. But
19 I -- I don't have that off the top
20 of my head.

21 BY MR. VAUGHN:

22 Q. So you do think that there
23 are some substances that can inhibit 2E1?

24 A. Maybe.

1 Q. Maybe. What about
2 phytochemicals?

3 A. I'm not sure what you're
4 referring to.

5 Q. Chemical compounds produced
6 by plants. Are you aware of any
7 compounds that plants could produce that
8 could inhibit 2E1?

9 A. If there is, I didn't look
10 at that or I didn't consider it.

11 Q. Okay. Doctor, plaintiffs'
12 experts have opined that NDMA and cancer
13 have a linear dose-response with no dose
14 threshold. You disagree with that
15 opinion, correct?

16 MS. KAPKE: Object to form.

17 THE WITNESS: I disagree
18 with the latter part of that
19 conclusion about no dose
20 threshold, because that's not
21 consistent with the data that I've
22 included in my report.

23 BY MR. VAUGHN:

24 Q. Okay. Have you seen any

1 evidence or literature suggesting that
2 there is a no-dose threshold?

3 A. Yes. I refer in my
4 report -- excuse me. The Ito study.

5 Q. You said Ito?

6 A. I-T-O.

7 Q. Okay. Ito. Gotcha.

8 A. There was a noneffective
9 level of carcinogenesis at .1 milligrams
10 per kilogram by the oral route.

11 Q. Is that the only thing that
12 you're basing your opinion off of?

13 A. No.

14 Q. What else?

15 A. One of the Peto studies on
16 Page 34. The apparent increase in liver
17 cancer was only seen in doses above
18 .3 parts per million, equating to
19 15 micrograms per kilogram per day.

20 Q. So you actually relied on
21 Peto to say there is no dose-response --
22 or there is no -- I'm sorry, there is no
23 dose threshold?

24 MS. THOMPSON: Objection to

1 form.

2 THE WITNESS: I'm relying on
3 that particular Peto study. And
4 this is in -- this is in comparing
5 against his rate of nontreated
6 rats who also developed liver
7 cancer.

8 So evidence of higher doses,
9 yes, but not at the dose different
10 from what was seen in the
11 background noise of his rat
12 population.

13 BY MR. VAUGHN:

14 Q. Do you know if Peto believes
15 there is a no-dose threshold?

16 A. I may --

17 MS. THOMPSON: Object to the
18 form. Sorry.

19 THE WITNESS: Yeah, I may
20 have mentioned it in my report
21 that he uses terms about the
22 likely shapes of dose-response.
23 And that's on Page 36 in my
24 report.

1 "In Peto's conclusion is the
2 comment, 'General arguments about
3 the likely shapes of dose-response
4 relationships make it probable,
5 even at lower doses where direct
6 observation is impractical, that
7 this linear relationship may
8 remain approximately true for
9 Colworth rats, if not for
10 humans.' "

11 And so he's not sure at the
12 low doses if there's enough
13 evidence to solidly state that
14 there is a linear relationship.

15 BY MR. VAUGHN:

16 Q. He's not 100 percent sure,
17 but he thinks it's probable, correct?

18 A. He think it's possible,
19 probable. I'm just saying that the
20 people who do those studies are not
21 100 percent convinced at the low doses.

22 Q. They are not 100 percent.
23 But they think it's probable, correct?

24 MS. THOMPSON: Objection to

1 form.

2 THE WITNESS: That's not the
3 word he used. He said
4 "approximately true." So he
5 didn't use the word "probable."
6 That was your word.

7 BY MR. VAUGHN:

8 Q. Approximately true. Oh.
9 Would you at least think that's more
10 likely than not?

11 A. I do not know what he meant
12 by that.

13 Q. Okay.

14 A. And what it does mean is
15 that he can draw through the numbers and
16 call it a straight line, but that doesn't
17 mean that it actually describes what
18 happens at low doses like we're talking
19 about because he didn't do enough animals
20 and you don't see enough cancer at those
21 doses to have reliability.

22 And one of his areas of
23 statistical analysis in that study
24 involved something called his Z value.

1 And I go onto describe on
2 the next page, in his methodology, the Z
3 value, if it's between -- between the
4 numbers two and three, then judgment as
5 to how likely it is that treatment really
6 did cause the disease of interest becomes
7 more difficult.

8 And so he's unclear as well,
9 because in the ones that we are talking
10 about at these doses we're talking about
11 were in that range of uncertainty with
12 that Z value between two and three.

13 Q. Again, when you say he's not
14 sure, do you mean that, you know, he's --
15 what was the word you used, approximately
16 true?

17 A. That was his previous
18 statement.

19 Q. So you rely on Peto to say
20 that there is a threshold, but you
21 disagree with Peto's analysis of his own
22 studies?

23 A. I do not -- sorry.

24 MS. THOMPSON: Objection to

1 form.

2 THE WITNESS: I do not
3 disagree. That's not what I said.

4 I said he is unsure at those
5 low doses. And I am agreeing with
6 him at those low doses about the
7 uncertainty of a linear
8 relationship at doses that low.

9 BY MR. VAUGHN:

10 Q. Do you agree with him that
11 it's approximately true?

12 A. I agree that he can draw a
13 line through them and then claim that's
14 approximately true.

15 And I would just like to add
16 that this is an era at the time where
17 everyone pretty much already believed
18 that it was linear. And so to me, he was
19 trying to not accept that it might not
20 be.

21 And I think there are other
22 experts in this field who might argue
23 that we have more modern data that
24 dispute a low range linearity

1 relationship.

2 Q. Approximately what year was
3 Peto's study going on?

4 A. 1991 for this one. So
5 30 years ago.

6 Q. If you didn't know what Peto
7 meant by approximately true, wouldn't you
8 want to see what he meant by that
9 wording?

10 MS. THOMPSON: Objection.
11 Form.

12 THE WITNESS: I think if he
13 was able to give more detail on
14 what he meant, he would have put
15 it in his paper. So I'm only
16 going on what he put on his paper.

17 BY MR. VAUGHN:

18 Q. Have you not reviewed any of
19 Peto's other papers where he says that
20 there's likely no threshold for NDMA?

21 A. I have read his other
22 papers.

23 Q. And do you recall him saying
24 that it is likely there is no threshold

1 for NDMA?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I recall him
5 saying that. But that's not what
6 this study data shows.

7 BY MR. VAUGHN:

8 Q. And so are you disagreeing
9 with Peto that it is likely there is no
10 threshold for NDMA?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: Again, I'm
14 disagreeing that the data show
15 that. We're talking now about his
16 interpretation of his data at an
17 era where linearity was the
18 accepted, and which we now know is
19 not necessarily the case.

20 BY MR. VAUGHN:

21 Q. Can you explain to the jury
22 what a linear dose-response means?

23 A. In this case it means that
24 you can identify with dose increases

1 across a broad enough dose range that you
2 see an increase in the effect. And that
3 effect could be a positive effect or it
4 could be a negative effect.

5 And I think all of the
6 papers in this realm that talk about low
7 doses, that the effect rates are so small
8 that you start losing your reliability of
9 that linear relationship.

10 The Brantom study, which is
11 the next one at the bottom of Page 37, in
12 Brantom's introductory remarks he
13 considers the possibility that at very
14 low levels of exposure there is no
15 effect.

16 And he did essentially a
17 similar study to what Peto did.

18 Q. He considers the
19 possibility. Is that what you said?

20 A. That's a quote in my -- in
21 my report from what he says in the
22 introductory components to his thesis
23 project.

24 Q. So he thinks there's some

1 possibility that there might not be a
2 threshold?

3 MS. THOMPSON: Objection.
4 Form.

5 THE WITNESS: That's what he
6 says.

7 BY MR. VAUGHN:

8 Q. But you're convinced there
9 is a threshold?

10 MS. THOMPSON: Objection.
11 Form.

12 THE WITNESS: I believe
13 there is a threshold, yes.

14 BY MR. VAUGHN:

15 Q. And so is it your opinion
16 that you can consume a certain amount of
17 NDMA per day and not be at any increased
18 risk of developing cancer, but once you
19 pass some threshold, then boom, you can
20 start developing cancer?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: That would
24 mischaracterize what I've written

1 in my report.

2 BY MR. VAUGHN:

3 Q. How did I mischaracterize
4 it?

5 A. I have identified a level
6 below which, number one, there does not
7 appear to be proof of a cancer effect,
8 again, in rat studies. And that I
9 further go on to say that's consistent
10 with first-pass metabolism at low doses
11 of this kind of compound, and that these
12 reported no cancer rates are hundreds to
13 thousands of times higher than the amount
14 of NDMA found in any of the valsartan
15 products.

16 Q. Based on your methodology,
17 correct?

18 A. Based on what's in the
19 literature.

20 Q. Okay. But, I mean, the dose
21 comparison, you're the one that did that
22 calculation, right?

23 A. I did. But I didn't create
24 the noncancer dose that I'm reporting

1 from these studies like Ito.

2 Q. But to take the animal dose
3 to get the human dose, you're the one
4 that did that math, right?

5 A. Yes.

6 Q. All right. And we'll get to
7 your methodology on that later.

8 In your opinion, what is the
9 threshold level of NDMA that is needed to
10 increase a human's risk of getting
11 cancer?

12 MS. THOMPSON: Objection.
13 Form. Asked and answered.

14 THE WITNESS: I do not know
15 that dose. As I've said
16 previously, I'm able to identify
17 what appears to be a dose below
18 which you don't see cancer. I
19 don't have the ability to identify
20 above which, because at these low
21 dose exposure levels that seem
22 they don't cause cancer or that do
23 not cause cancer in animal
24 studies, often the next dose is

1 100 or a thousand times.

2 So there may be something in
3 between. I don't know where that
4 is.

5 So I'm only talking about
6 the no effect dose. I'm not
7 trying to describe or define the
8 effect dose.

9 BY MR. VAUGHN:

10 Q. Is this mysterious threshold
11 for NDMA in humans, is it the exact same
12 for every person?

13 MS. THOMPSON: Objection.
14 Form.

15 THE WITNESS: Since I don't
16 know what it is, I can't answer
17 that.

18 BY MR. VAUGHN:

19 Q. Is it your opinion that once
20 that threshold is crossed, the
21 dose-response then would be linear from
22 then on?

23 MS. THOMPSON: Objection.
24 Form.

1 THE WITNESS: That's not
2 what I said.

3 What I said is the amount of
4 NDMA in any valsartan product is
5 hundreds to thousand times below
6 doses that are no cancer related
7 in the rat studies.

8 BY MR. VAUGHN:

9 Q. I'm sorry. I wasn't clear
10 in my question probably.

11 Valsartan aside. If you're
12 giving a human NDMA, once you pass
13 whatever that threshold is, is the
14 dose-response going to be linear?

15 A. We don't know that in
16 humans. I have no idea. There's never
17 been a --

18 Q. Is there a chance that it
19 becomes exponential at some point, it
20 kind of goes straight up?

21 A. I have no idea.

22 MS. THOMPSON: Objection.

23 BY MR. VAUGHN:

24 Q. What -- how do you define

1 whether you have a linear dose-response?
2 What does the word "linear" in the
3 dose-response mean?

4 A. It depends on what the
5 response is.

6 Q. Can you explain that to me,
7 what you mean?

8 A. Well, which response are we
9 talking about?

10 Q. Well, let's talk about NDMA
11 and its ability to increase the risk of
12 cancer. So what is a linear
13 dose-response mean in that context?

14 A. In that context it's defined
15 a couple of different ways.

16 Pegg defined it by looking
17 at the formation of adducts.

18 Peto defined it by the
19 formation of tumors so there are
20 different ways of defining that.

21 Q. But the linear part of it,
22 what does that mean? Does that mean,
23 like, it's proportional to the amount
24 that you increase the dose to increase

1 risk of cancer? Is that what's going on
2 with linear?

3 A. Again, the use of the term
4 linear means as the dose goes up, it
5 looks like the occurrence goes up, which
6 may or may not necessarily be
7 characterized as a dead straight line.
8 They just sort of observe that there's
9 more when they sort of plot it over time.

10 Q. Is there a reason that
11 throughout your entire expert report you
12 never mention that NDMA is genotoxic?

13 MS. THOMPSON: Objection.
14 Form.

15 THE WITNESS: There's no
16 reason that I didn't mention it.
17 It was not what I was focused on
18 in my report.

19 BY MR. VAUGHN:

20 Q. Do you know if NDMA is
21 genotoxin?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: We know it is

1 in animals.

2 BY MR. VAUGHN:

3 Q. Do you know if a substance
4 being a genotoxin impacts its dose
5 threshold?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: I don't even
9 understand the question. So I'm
10 not sure how to answer it.

11 BY MR. VAUGHN:

12 Q. Okay. So you didn't
13 consider the fact that NDMA is a
14 genotoxin when coming to your opinions
15 that there is a threshold for NDMA
16 exposure before it's going to increase
17 the risk of cancer, correct?

18 A. Well, not correct, because
19 that's not what I testified.

20 I'm not defining, again, the
21 threshold at which genotoxicity occurs.
22 That wasn't the focus of my report.

23 Q. There's -- I think you kind
24 of misconstrued things. I don't think

1 there's a threshold for genotoxicity.

2 NDMA is just a genotoxin, period,

3 correct?

4 A. Yes, it's a genotoxin.

5 Q. At any amount given, right?

6 A. Well, I don't know about
7 that. That sort of gets out of my area
8 of testimony, because there are
9 oncologists and toxicologists that that's
10 more within their realm.

11 I'm more looking at more
12 dose-response relationships at what
13 appear to be safe levels of NDMA and how
14 that compares to the amount of NDMA found
15 in valsartan products.

16 Q. And so you would defer to an
17 oncologist or a toxicologist on if the
18 genotoxicity of a substance would impact
19 it's dose threshold?

20 MS. THOMPSON: Objection.

21 THE WITNESS: Not
22 necessarily, but again, I don't
23 know that I understand what that
24 question was asking.

1 BY MR. VAUGHN:

2 Q. Do you know or have you seen
3 any literature that says that you should
4 calculate the dose-response or the
5 threshold differently if the substance is
6 a genotoxin?

7 MS. THOMPSON: Objection.
8 Form.

9 THE WITNESS: Characterizing
10 dose-response relationships has
11 nothing to do with whether a
12 chemical or a drug is genotoxic or
13 not.

14 BY MR. VAUGHN:

15 Q. What about dose threshold?

16 A. Again, depends on the
17 response. But there are many drugs where
18 you calculate a dose threshold that has
19 nothing to do with genotoxicity.

20 Q. There are many drugs that
21 you can calculate -- sorry, scratch that.

22 Can you name one genotoxin
23 that has a threshold level needed to --
24 scratch that again. I'm sorry.

1 Can you name one genotoxin
2 that has a dose threshold?

3 MS. THOMPSON: Objection.
4 Form.

5 THE WITNESS: A dose
6 threshold for what?

7 BY MR. VAUGHN:

8 Q. Before it can cause cancer.

9 A. No. I mean, that's what I
10 previously testified is that I'm not here
11 today to try to define the genotoxic dose
12 threshold that starts causing
13 genotoxicity. That's not the nature of
14 my report.

15 Q. Then how can you say that
16 there is a dose threshold for NDMA?

17 A. And I'll say again, it's the
18 dose from the studies that was shown to
19 not be genotoxic.

20 Q. And so that's all that you
21 base your opinion on, correct?

22 A. That is what I'm basing my
23 opinion on.

24 Q. Thank you. Can you define

1 genotoxic to the jury for me?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I don't think
5 that's my role to do that.

6 Again, I'm focusing on drug
7 metabolism. I think there are
8 others who have spent time on
9 toxicity, genotoxicity,
10 mutagenicity. They're better
11 equipped to do that than I am. So
12 it's not my role.

13 BY MR. VAUGHN:

14 Q. And you would defer to them,
15 correct?

16 A. In the definition of
17 genotoxicity, yes, I would.

18 Q. And that's the only aspect
19 that you would defer to them on, is just
20 the definition?

21 MS. THOMPSON: Objection.

22 Form.

23 THE WITNESS: I never said
24 it was the only aspect I would

1 refer to them on. I said that
2 specific question is one that I
3 think it's -- I would defer to
4 them.

5 BY MR. VAUGHN:

6 Q. Do you know if a genotoxin
7 can permanently alter a person's DNA?

8 MS. THOMPSON: Objection.
9 Form.

10 THE WITNESS: I have no
11 opinion on that.

12 BY MR. VAUGHN:

13 Q. So you have no definition of
14 genotoxicity?

15 MS. THOMPSON: Objection.
16 Form.

17 THE WITNESS: I do not.

18 BY MR. VAUGHN:

19 Q. And I assume you probably
20 have no opinion if it does permanently
21 mutate someone's DNA, if that can be
22 passed to every generation thereafter?

23 MS. THOMPSON: Objection.
24 Form.

1 THE WITNESS: I do not have
2 an opinion on that.

3 BY MR. VAUGHN:

4 Q. Let's go to Page 26 of your
5 expert report. The first paragraph at
6 the bottom, if you can read us the first
7 sentence that starts with, "The alpha."

8 A. "The alpha-hydroxylation
9 pathway produces the methyldiazonium ion,
10 which binds with a segment of DNA to
11 produce a primary mutagenic and
12 carcinogenic substance
13 O6-methyl-guanine."

14 Q. Can you explain what that
15 means to the jury?

16 A. Well, to me, what it means
17 particularly if you put it in the context
18 of the following sentence, is that the
19 key step in producing the potential
20 mutagenic carcinogenic substance is
21 forming the alpha-hydroxylated metabolite
22 of NDMA, which is 2E1-mediated.

23 Q. Is it okay if we refer to
24 this as O6 going forward?

1 A. Sure.

2 Q. It's a lot to say. Thank
3 you. And so you would agree that O6 is a
4 carcinogen, correct?

5 MS. THOMPSON: Objection.
6 Form.

7 THE WITNESS: That is the
8 known carcinogen, correct.

9 BY MR. VAUGHN:

10 Q. And so O6 is not a probable
11 human carcinogen. O6 is a known human
12 carcinogen, correct?

13 MS. THOMPSON: Objection to
14 form.

15 THE WITNESS: Incorrect. We
16 do not know the known carcinogenic
17 effect of NDMA or its downstream
18 metabolites.

19 BY MR. VAUGHN:

20 Q. Why did -- in your report,
21 do you note that O6 is a carcinogenic
22 substance?

23 A. Because it caused cancer in
24 animals.

1 Q. Oh, so you're talking about
2 animals. You are not talking about
3 humans?

4 A. Yes.

5 Q. You think O6 is unlikely to
6 cause cancer in humans?

7 MS. THOMPSON: Objection.
8 Form.

9 THE WITNESS: I never said
10 that. I think that's, again, a
11 better question for toxicology
12 oncology. The amounts, the
13 mechanism, the inherent protective
14 mechanisms. That's not the nature
15 of my testimony.

16 BY MR. VAUGHN:

17 Q. The amount, you would defer
18 to a toxicologist or an oncologist, is
19 what you just testified to, correct?

20 MS. THOMPSON: Objection to
21 form.

22 THE WITNESS: The amount
23 that would make it a carcinogen in
24 animals, yes.

1 BY MR. VAUGHN:

2 Q. And in humans?

3 A. I don't have to defer to
4 anybody on that one because it's never
5 been studied, so it's not known.

6 Q. Okay. But at least in
7 animals, you would defer to an oncologist
8 or toxicologist on how much of a dose is
9 necessary to induce cancer, correct?

10 MS. THOMPSON: Objection.

11 Form.

12 THE WITNESS: Correct. As
13 I've stated before, it was not the
14 intent of my report to define that
15 threshold.

16 My point was to find the
17 threshold below which there
18 doesn't appear to be a cancer
19 risk.

20 BY MR. VAUGHN:

21 Q. Okay. So would you also
22 defer to a cancer researcher on what dose
23 would cause cancer or could increase the
24 risk of cancer?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: That's what I
4 said, yes.

5 BY MR. VAUGHN:

6 Q. All right. She objected.
7 Let me ask it again so it's really clear.

8 In regards to the dose
9 necessary for NDMA to increase the risk
10 of cancer, you would defer to a cancer
11 researcher, correct?

12 MS. THOMPSON: Objection.
13 Form.

14 THE WITNESS: It's not the
15 nature of my testimony.

16 BY MR. VAUGHN:

17 Q. And so you would defer to a
18 cancer researcher, correct?

19 A. Potentially. Could be
20 toxicologist. Could be somebody else.
21 But it's not the nature of my testimony.

22 Q. Let's go to Page 33 of your
23 report now.

24 So towards the bottom of

1 this page, you opine that the liver may
2 have a carcinogenic surveillance system
3 that removes O6 from DNA prior to
4 carcinogenesis.

5 Is this opinion based on the
6 Pegg paper that you cited above?

7 A. Pegg refers to it in his
8 paper. There are many others that I came
9 across that refer to that too. And the
10 surveillance system is my own sort of
11 selection of a descriptor.

12 Q. Do you find Pegg to be
13 reliable?

14 A. Yes.

15 Q. Your opinion regarding the
16 surveillance system being able to remove
17 O6 from DNA prior to carcinogenesis, is
18 that opinion specific to the liver?

19 A. In the context of what my
20 report is, I'm referring to the liver's
21 ability to protect itself against
22 potential carcinogens from NDMA, again
23 depending on the dose.

24 My understanding, although

1 it's not my area, is that that
2 surveillance system is essentially in all
3 tissues, in all cells.

4 Q. And so you agree that this
5 surveillance system opinion is really not
6 in your wheelhouse, correct?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: It's in my
10 wheelhouse in the context of how I
11 used it. I'm not trying to
12 quantify it.

13 I find it from a
14 pharmacologic sense interesting
15 that the lower dose NDMA, because
16 of first-pass metabolism and
17 clearance, 2E1 produces the
18 potential carcinogen in the very
19 organ that has the best probable
20 capacity to remove it.

21 BY MR. VAUGHN:

22 Q. And so if NDMA were to have
23 a high bioavailability in humans and was
24 able to get past the liver, the liver's

1 carcinogenic surveillance system wouldn't
2 have any impact on the O6 formations in
3 other organs or tissues, correct?

4 MS. THOMPSON: Objection.
5 Form.

6 THE WITNESS: Again, that's
7 a hypothetical. That's not what
8 I'm dealing with because we're not
9 giving those kinds of doses to
10 humans.

11 BY MR. VAUGHN:

12 Q. You are an expert in this
13 litigation, so I can ask you a
14 hypotheticals.

15 And I'm saying
16 hypothetically, if it were to get past
17 the liver, the liver surveillance system
18 wouldn't have any impact on those O6
19 formations in other tissues and organs,
20 correct?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: Yeah, if you
24 were to give some massive

1 overdose, then I guess, in theory,
2 in your hypothetical, you could
3 bypass the liver.

4 BY MR. VAUGHN:

5 Q. But you don't know what dose
6 that is, correct?

7 A. I do not.

8 Q. Okay. Are you aware --
9 sorry.

10 Are you aware of any factors
11 that can inhibit or increase the
12 metabolism of NDMA in the liver?

13 MS. THOMPSON: Objection.
14 Form.

15 THE WITNESS: The only one
16 that I looked at, because of my
17 interest in pharmacogenomics, is
18 to see if there is any 2E1 related
19 polymorphisms. And those have not
20 been identified. So no.

21 BY MR. VAUGHN:

22 Q. And so in coming to your
23 opinions in this case, you did not
24 consider any factors that could inhibit

1 or increase the metabolism of NDMA in the
2 liver?

3 MS. THOMPSON: Objection.

4 THE WITNESS: In the
5 research that I did, if I came
6 across it, then I would have
7 commented on it. So it wasn't
8 that I didn't consider it. I
9 would have looked for it in the
10 articles that I was looking at.

11 BY MR. VAUGHN:

12 Q. And you didn't comment
13 anywhere in your expert report on it, did
14 you?

15 A. I did not.

16 Q. Did you actually read the
17 Pegg paper?

18 A. I did.

19 MR. VAUGHN: Hey, Tyler, can
20 you pull up the 1980 Pegg paper
21 for us.

22 (Document marked for
23 identification as Exhibit
24 Bottorff-4.)

1 MR. VAUGHN: Go to PDF Page
2 15.

3 BY MR. VAUGHN:

4 Q. All right. And that second
5 sentence, can you read that aloud for the
6 jury, please, where it starts, "For
7 example."

8 A. "For example, when the
9 ability of the liver to metabolize NDMA
10 is impaired by feeding a
11 protein-deficient diet, a greater
12 fraction of the carcinogen may become
13 available for reaction with other
14 organs."

15 Q. Why did you not mention that
16 in your expert report?

17 MS. THOMPSON: Objection.
18 Form.

19 THE WITNESS: I have no
20 reason for that. But again, the
21 impact of that would have to also
22 depend on the dose.

23 And so, I didn't consider it
24 as having an impact on the doses

1 that we're talking about.

2 BY MR. VAUGHN:

3 Q. Why didn't you mention that
4 in your expert report? I thought you
5 said you would have addressed it?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: Because I
9 didn't think it would have an
10 impact at the amount of doses that
11 we are talking about.

12 BY MR. VAUGHN:

13 Q. Well, that's not the answer
14 that you gave me a second ago, is it?

15 MS. THOMPSON: Objection.

16 Form.

17 BY MR. VAUGHN:

18 Q. Go ahead and read the next
19 sentence. Starts also. "Also since
20 uptake."

21 Can you read that for the
22 jury?

23 MS. THOMPSON: Can he answer
24 the question that you had earlier

1 before we --

2 MR. VAUGHN: I'm sorry. I
3 thought he -- yeah, absolutely.

4 MS. THOMPSON: Okay. We may
5 need the court reporter to read it
6 back. But I think you asked an
7 question and then he didn't
8 answer --

9 MR. VAUGHN: I can ask it
10 again.

11 BY MR. VAUGHN:

12 Q. That was not the answer that
13 you gave earlier, was it?

14 MS. THOMPSON: Objection.
15 Form.

16 Go ahead.

17 THE WITNESS: And I think I
18 said that if it would have
19 impacted my opinions, I would have
20 included it. And so it didn't
21 impact my opinion.

22 BY MR. VAUGHN:

23 Q. I thought you said if you
24 would have read it in the literature you

1 would have addressed it in your expert
2 report.

3 MS. THOMPSON: Objection to
4 form. Mischaracterizes.

5 THE WITNESS: If it would
6 have impacted my opinion.

7 BY MR. VAUGHN:

8 Q. And again, you haven't
9 reviewed all the internal testing on the
10 levels of NDMA in valsartan, have you?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: No, I haven't.

14 BY MR. VAUGHN:

15 Q. Okay. I'm going to now ask
16 you if you can read that next sentence
17 that starts with "Also, since uptake."

18 A. "Also, since uptake of NDMA
19 is more rapid from the small intestine
20 than from the stomach, agents that retard
21 gastric emptying might be expected to
22 slow the rate of absorption."

23 Q. What does "retard gastric
24 emptying" mean?

1 A. Slow gastric emptying into
2 the site of absorption.

3 Q. Okay. Can you read the next
4 sentence for me?

5 A. "Agrelo have recently
6 published data which show that the
7 presence of fat retards the rate of
8 uptake and the metabolism of oral doses
9 of NDMA."

10 Q. And you --

11 A. And he -- I'm sorry.

12 Then he goes on to say that
13 that might actually increase its
14 metabolism by the liver, not enhance its
15 ability to escape the liver.

16 Q. And you didn't mention that
17 in your report either, did you?

18 MS. THOMPSON: Objection.

19 Form.

20 THE WITNESS: No. Again,
21 these aren't things that I
22 considered. He was being thorough
23 in looking at potentials.

24 But most of these would have

1 effects, based on my knowledge of
2 these issues with other drugs that
3 would not be -- that would not
4 alter my opinion about NDMA in the
5 doses that we are talking about.

6 BY MR. VAUGHN:

7 Q. Do you know if a person's
8 liver would metabolize NDMA with the same
9 efficiency if the person took their
10 valsartan with just water versus taking
11 their valsartan with food or drinks other
12 than water?

13 MS. THOMPSON: Objection.
14 Form.

15 THE WITNESS: I'm sorry,
16 effect their absorption of what?

17 BY MR. VAUGHN:

18 Q. Do you know if a person's
19 liver would metabolize NDMA at the same
20 efficiency regardless if the patient took
21 the valsartan with water or if they took
22 it with food or if they took it with a
23 drink other than water?

24 MS. THOMPSON: Object to

1 form.

2 THE WITNESS: We -- sorry.

3 We don't know that.

4 BY MR. VAUGHN:

5 Q. We don't -- who is we?

6 A. We, us, all of us. Nobody
7 knows that answer.

8 Q. Are you speaking for the
9 plaintiffs' experts as well?

10 A. Well, let me rephrase my
11 answer then.

12 There are no data in humans
13 that address that question that you
14 asked.

15 Q. What about animals?

16 A. I mean, you could talk about
17 what he says here. I don't think they
18 have a substantial effect at the doses
19 we're talking about.

20 Q. What do you base that on?

21 A. Just that these doses are so
22 small and generally these sort of
23 theoreticals don't have that much of an
24 impact.

1 Q. And again, these doses that
2 are so small, you're not even aware of
3 the highest doses, are you?

4 MS. THOMPSON: Objection.
5 Form. Asked and answered.

6 THE WITNESS: I'm aware of
7 the highest doses that I had
8 access to.

9 BY MR. VAUGHN:

10 Q. Do you know if vitamins can
11 impact the carcinogenicity of NDMA or
12 NDEA in animals or humans?

13 MS. THOMPSON: Objection to
14 form.

15 THE WITNESS: I have not
16 looked at that.

17 BY MR. VAUGHN:

18 Q. Being a vegetarian, would
19 that have any impact on how efficiently
20 someone's liver can metabolize NDMA?

21 MS. THOMPSON: Objection to
22 form.

23 THE WITNESS: I have no
24 opinion on that.

1 BY MR. VAUGHN:

2 Q. Same thing with a high-fat
3 diet. You have no opinion on that if
4 it's going to impact the rate of
5 metabolism of NDMA in a human liver?

6 A. I have no -- no opinion.

7 Q. Same with alcohol, no
8 opinion on if that's going to impact the
9 metabolism of NDMA in a human?

10 A. Correct.

11 Q. So is your opinion regarding
12 NDMA in valsartan, how it's going to be
13 metabolized, based on the assumption that
14 nothing else can impact the metabolism?

15 MS. THOMPSON: Objection.
16 Form.

17 THE WITNESS: Let me put it
18 back into perspective that as my
19 approach.

20 Again, in the doses that do
21 not appear to be carcinogenic in
22 animals, which is hovering around
23 .1 milligrams per kilogram or
24 lower, that that threshold, which

1 is not the carcinogenic threshold,
2 it's the non-carcinogenic
3 threshold, is in the range of 350
4 to 21,000 times higher than the
5 valsartan I evaluated as having
6 contained those amounts of NDMA.

7 And so, if gastric emptying
8 or taking a glass of water versus
9 a glass of milk, there's never
10 been any bioavailability study
11 with any drug under any of those
12 conditions that has changed
13 absorption by 350 times or, you
14 know, 22,000 times.

15 So these issues that
16 might -- in Pegg's paper where I
17 think he was being thorough in all
18 the data he analyzed, in my
19 opinion, having read this, it had
20 no impact on my conclusion.

21 So I didn't put it in the
22 paper for that reason.

23 BY MR. VAUGHN:

24 Q. Your paper is not as

1 thorough as Pegg's?

2 MS. THOMPSON: Is that a
3 question or a statement?

4 MR. VAUGHN: It's a
5 question.

6 MS. THOMPSON: Objection.
7 Form.

8 THE WITNESS: My paper is
9 focused on what I focused on. His
10 paper focused on other things.

11 BY MR. VAUGHN:

12 Q. In your opinion, is
13 100 percent of NDMA absorbed and makes
14 its way to the liver?

15 MS. THOMPSON: Objection.
16 Form.

17 THE WITNESS: Do you mean
18 given orally?

19 BY MR. VAUGHN:

20 Q. Correct.

21 A. Because inhaled --

22 Q. No, I understand. I
23 appreciate your clarification. I'll
24 re-ask the question.

1 Is it your opinion that when
2 NDMA is ingested orally, that 100 percent
3 of it makes its way to the liver?

4 A. Yes. I think there are
5 bioavailability studies in animals that
6 show that.

7 Q. So none of it is going to be
8 excreted through the feces or make it
9 down that tract?

10 A. No. I think the study I
11 saw, the absorption was 90-something
12 percent.

13 Q. Does the stomach have P450
14 in it?

15 A. It does. The only two
16 enzymes that I've seen in the stomach are
17 like 2J2 and 2S4, or something.

18 So very, very, very uncommon
19 P450s, but not the ones we are talking
20 about.

21 Q. What about in the
22 intestines, large intestine, small
23 intestine? Do they have P450-2E1?

24 A. Actually, they do not. The

1 small intestine does not have 2E1.

2 Q. A second ago, did you say
3 that you saw a study that said 90 percent
4 was absorbed?

5 A. I believe that's the one
6 that I saw where they gave administration
7 through a feeding tube into the stomach
8 and then also down into the intestine.

9 Q. So that's not 100 percent.
10 Where's that other ten percent going?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: They just
14 couldn't measure it anymore from
15 drawing back from the tube.

16 BY MR. VAUGHN:

17 Q. Is there a chance that some
18 of it would be excreted to the feces?

19 A. It hasn't been described.

20 Q. Do you know if the rectum
21 has P450-2E1?

22 A. I believe it does not. My
23 understanding is that as you go further
24 down from the small intestine towards the

1 larger intestine, that there's this
2 decline in all the P450s. And I have
3 never seen anything that identified 2E1
4 being in the colon or rectum.

5 Q. Does the entire GI tract
6 have P450 in it?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: Some have
10 P450, and some do not.

11 BY MR. VAUGHN:

12 Q. The study in which you were
13 saying 90 percent, what animal was that
14 in? Do you recall?

15 A. Pretty sure it was in rats.

16 Q. And was that an oral dose?

17 A. Yes. They put like a
18 feeding tube down and then administered
19 the NDMA through the feeding tube. And
20 then sampled back out of the feeding tube
21 over time to see how the drug was
22 absorbed.

23 Q. How does pulling it back out
24 let you know if it made it to the liver?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: There are
4 other studies showing that it goes
5 to the liver once it's absorbed in
6 the small intestine.

7 MR. VAUGHN: Can we go to
8 Page 19 -- actually, before we do
9 that, stay here.

10 Can we go to the bottom of
11 the summary of -- on this page,
12 yeah.

13 BY MR. VAUGHN:

14 Q. Then can you read the
15 sentence that starts with, "The greatest
16 capacity," and read that sentence and the
17 one afterward.

18 A. Yeah, I can see fine on
19 mine.

20 "The greatest capacity to
21 metabolize these nitrosamines to
22 alkylating agents is found in the liver,
23 but other organs including the esophagus,
24 lung and kidney are also capable of

1 activation."

2 Q. And the next sentence as
3 well, please.

4 A. "These organs may be more
5 susceptible to alkylation than the liver
6 because they have a lesser ability to
7 catalyze the removal of the
8 O6-alkyl-guanine from their DNA."

9 Q. Do you agree with that?

10 A. Particularly if you go on to
11 the next sentence, because I want to put
12 it in the proper context.

13 "However, orally
14 administered doses of NDMA and the NDMA
15 formed by nitrosation reactions" --

16 THE WITNESS: Can you keep
17 scrolling for me, please.

18 MS. THOMPSON: I don't have
19 control of the documents.

20 THE WITNESS: Oh, I'm sorry.

21 -- "within the GI tract are
22 rapidly absorbed from the upper
23 part of the small intestine and
24 carried to the liver in the portal

1 blood supply. When small doses
2 are given in this way, the
3 capacity of the liver to
4 metabolize the carcinogen is
5 sufficient that the nitrosamines
6 effectively cleared in a
7 first-pass effect, leaving very
8 little to interact with other
9 organs."

10 So to read those couple
11 sentences that you had me start
12 with, I think it was only fair to
13 put it into the context of the
14 rest of Pegg's comments.

15 BY MR. VAUGHN:

16 Q. No, actually. I'm really
17 glad that you did. At the end of that,
18 it said "very little is left to interact
19 with other organs."

20 You agree with that, right?
21 It's not that it's none left. It's just
22 not as much, right?

23 A. No, not right. It depends
24 on the dose.

1 Q. And here it says "when small
2 doses are given." Would you agree with
3 that? Small doses, you're still going to
4 get a little bit that goes to the other
5 organs?

6 A. Depends on --

7 MS. THOMPSON: Objection to
8 form.

9 Sorry.

10 THE WITNESS: Sorry.

11 It depends on how small the
12 dose.

13 BY MR. VAUGHN:

14 Q. Do you have any idea what
15 Pegg meant when he said small dose here?

16 A. No, he didn't define it in
17 this set.

18 Q. And we don't know if his
19 definition of small dose is the same as
20 your definition of a trace amount?

21 A. I don't.

22 Q. All right. Can we go back
23 to your expert report, and go to Page 19
24 now.

1 Can you read out loud the
2 first full sentence on this page? It
3 starts at the end of Line 117.

4 MS. THOMPSON: Line 117?

5 MR. VAUGHN: I messed up on
6 that. 317.

7 It starts with the word
8 "only." Sorry about that.

9 MS. THOMPSON: Here, if it's
10 easier to read.

11 THE WITNESS: I've go it.

12 "Only when the dose exceeds
13 first-pass metabolism capacity
14 will unchanged drug or compound be
15 systemically available for
16 distribution through the
17 bloodstream, leaving the liver and
18 being delivered to other tissues
19 and organs."

20 BY MR. VAUGHN:

21 Q. And so is it your opinion
22 that if a human orally ingests NDMA, that
23 it would only be detectable in the blood
24 if it was exceeding the first-pass

1 metabolism capacity of the liver?

2 A. Correct.

3 Q. Do you agree that if NDMA
4 reaches the bloodstream, that it has the
5 potential to cause cancer in numerous
6 organs and tissues?

7 MS. THOMPSON: Objection.

8 Form.

9 THE WITNESS: Again, I think
10 we've talked about this a few
11 times.

12 It depends on the amount,
13 how much gets past the liver. And
14 the ability of that organ to
15 generate -- or to have the 2E1.

16 So it's dependent on a lot
17 of things.

18 BY MR. VAUGHN:

19 Q. And again, you've stated
20 several times that you're not here to
21 talk about what dose is necessary.

22 So dose aside, if you're
23 getting into the bloodstream there's more
24 organs and tissues at risk, correct?

1 MS. THOMPSON: Object to
2 form.

3 THE WITNESS: There's --
4 there's more organs and tissue
5 that can receive the drug. I
6 don't know what that risk is
7 because it depends on the amount.

8 BY MR. VAUGHN:

9 Q. I mean, the risk of it would
10 be getting cancer. Are you saying that
11 you don't know how likely they are to get
12 cancer?

13 A. Yes.

14 MS. THOMPSON: Object to
15 form.

16 THE WITNESS: I can't
17 quantify without having a dose
18 to -- or an amount that gets to
19 the organ or knowing which organ
20 and how much 2E1 it has and how
21 much of a removal system that it
22 has.

23 Those are -- those are all
24 things that would impact the

1 conclusion you were drawing.

2 BY MR. VAUGHN:

3 Q. Are you aware if some people
4 are exposed to NDMA in their diet?

5 A. I am aware of that.

6 Q. Do you know what the average
7 amount of NDMA that -- scratch that. One
8 second.

9 Do you know what the average
10 amount of NDMA an American is exposed to
11 in their diet every day?

12 MS. THOMPSON: Objection to
13 form.

14 THE WITNESS: I recall
15 having seen it.

16 My recollection is that it
17 might be like a few hundred
18 nanograms or up to maybe a tenth
19 of a microgram or something like
20 that.

21 BY MR. VAUGHN:

22 Q. It's kind of impossible to
23 not be exposed to NDMA at all as a human,
24 correct?

1 A. I would say that the sources
2 of NDMA that I've read about that are in
3 dietary substances, some or many of them
4 are part of the normal American diet,
5 yes.

6 Q. Is it your opinion that NDMA
7 in the diet can't cause cancer in humans?

8 MS. THOMPSON: Objection to
9 form.

10 THE WITNESS: It is my
11 opinion that looking at the
12 dietary studies that have been
13 done, I don't believe they
14 reliably and consistently show
15 that they have caused cancer
16 through dietary studies.

17 BY MR. VAUGHN:

18 Q. But they do show an
19 association, correct?

20 MS. THOMPSON: Objection to
21 form.

22 THE WITNESS: Sorry. An
23 association, yes.

24 BY MR. VAUGHN:

1 Q. I want to ask you again your
2 opinion. Can the amount of NDMA in the
3 diet increase the risk of cancer in
4 humans?

5 MS. THOMPSON: Objection to
6 form.

7 THE WITNESS: And I'm saying
8 that hasn't been demonstrated. If
9 it had been, it would have a
10 different IARC classification than
11 it does.

12 BY MR. VAUGHN:

13 Q. You're saying the amount of
14 NDMA in the diet probably could increase
15 the risk of cancer in humans?

16 A. No, I'm not saying that.
17 I'm saying there's no data that it does
18 increase cancer in humans.

19 Q. There's no data at all?

20 A. There are no data that prove
21 that NDMA in the diet causes cancer in
22 humans.

23 Q. And so prove. Again, like,
24 you're putting this at 100 percent

1 standard, right?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I don't
5 believe it's been proven. The
6 preponderance of the data are
7 conflicting to me.

8 BY MR. VAUGHN:

9 Q. Does it lean more one way or
10 the other?

11 MS. THOMPSON: Objection to
12 form.

13 THE WITNESS: Not in any
14 type of reliable conclusion that
15 I've been able to make, no.

16 BY MR. VAUGHN:

17 Q. So I'm okay to start eating
18 a lot of bacon with my whiskey again?
19 It's not going to increase my risk of
20 cancer?

21 MS. THOMPSON: Objection to
22 form.

23 BY MR. VAUGHN:

24 Q. I'd like to be able to do

1 that again. That's -- I really like
2 bacon.

3 A. On your grilled hamburger,
4 yes.

5 MR. VAUGHN: Do you want to
6 take a break real quick. Is that
7 okay?

8 MS. THOMPSON: Sure.

9 THE VIDEOGRAPHER: The time
10 right now is 2:07 p.m. We're off
11 the record.

12 (Short break.)

13 THE VIDEOGRAPHER: The time
14 right now is 2:23 p.m. We're back
15 on the record.

16 BY MR. VAUGHN:

17 Q. Doctor, if a human is able
18 to exceed their body's repair mechanisms
19 just through NDMA in their diet, then
20 wouldn't any additional amount of NDMA
21 further increase their risk of cancer?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: Again, I

1 suspect that's theoretically
2 possible, but --

3 BY MR. VAUGHN:

4 Q. What do you mean theoretical
5 possible?

6 A. Well they would have to --
7 well, number one, there's no proof in
8 humans that dietary NDMA causes cancer.

9 And so it's operating from
10 the assumption that it does, and so it
11 makes it hard for me to accept that
12 hypothetical.

13 Q. If an animal is able to
14 exceed their body's repair mechanisms
15 just through the NDMA in their diet, then
16 wouldn't any additional amount of NDMA
17 further increase that animal's risk of
18 cancer?

19 MS. THOMPSON: Objection.
20 Form.

21 THE WITNESS: So again, the
22 basis for that question was that
23 dietary NDMA is causing cancer in
24 animals?

1 BY MR. VAUGHN:

2 Q. Yeah. If/then. It's a
3 hypothetical?

4 A. I mean, same thing, it would
5 have to be enough to cause cancer to
6 begin with.

7 Q. And, again, hypothetical.
8 If that was enough, then any additional
9 amount of NDMA would further increase the
10 risk of cancer, correct?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: Well, I
14 believe the dose studies that have
15 given enough to cause cancer sort
16 of prove that that's possible.

17 BY MR. VAUGHN:

18 Q. Thank you, Doctor. Now, a
19 second ago you said the average amount
20 diet would have a few hundred nanograms
21 of NDMA in it a day. But what about a
22 single meal? Do you know how much that
23 on average would have?

24 MS. THOMPSON: Objection to

1 form. Scope.

2 THE WITNESS: I don't.

3 BY MR. VAUGHN:

4 Q. Less than a few hundred
5 nanograms, though, right?

6 MS. THOMPSON: Objection.

7 Form. Scope.

8 THE WITNESS: I mean, I
9 guess it depends on the meal
10 relative to the other meals of the
11 day. I mean, I don't know.

12 MR. VAUGHN: Tyler, can we
13 pull Pegg back up again, the 1980
14 Pegg study. Let's go to Page 15
15 again.

16 BY MR. VAUGHN:

17 Q. Doctor, that second
18 paragraph that starts with the word
19 "finally," can you read that aloud for
20 the jury?

21 A. "Finally, it has been
22 reported that NDMA and NDEA were present
23 in human peripheral blood samples and
24 that the amounts increased after a meal.

1 Calculations of total daily exposures
2 have been made on the basis of these
3 figures but without knowledge of the
4 clearance rate these calculations may be
5 seriously in error and may underestimate
6 total exposure."

7 Q. And so this is saying just
8 one meal is able to clear the liver and
9 get into the bloodstream, the NDMA; is
10 that correct?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: Again, I'd
14 have to look at those studies to
15 see if just that one-sentence
16 summary would be an accurate
17 representation.

18 BY MR. VAUGHN:

19 Q. Did you not look at those
20 two studies when you were forming the
21 basis of your opinions?

22 A. No, I did not.

23 Q. And so if this is true, that
24 a meal can -- levels of NDMA in a meal

1 can exceed what the liver can handle and
2 make it into the bloodstream, then if
3 someone took valsartan with NDMA in it,
4 that would also be able to make it into
5 the bloodstream, correct?

6 MS. THOMPSON: Objection.
7 Form.

8 THE WITNESS: Again, I can't
9 draw that same conclusion without
10 looking at those studies.

11 BY MR. VAUGHN:

12 Q. And you didn't look at those
13 studies, so you can't really opine on
14 what impact dietary NDMA is going to have
15 on the NDMA that's in valsartan, correct?

16 MS. THOMPSON: Objection.
17 Form.

18 THE WITNESS: No, I haven't
19 looked at these studies. So I
20 can't tell you what impact they
21 would have on my opinions.

22 BY MR. VAUGHN:

23 Q. What were the levels that
24 you were aware of, of NDMA in valsartan?

1 Was it 20,000 nanograms and they were
2 able to show 38,000 nanograms? Is that
3 what it says?

4 A. Yes.

5 Q. All right. And you said
6 that the average diet would have a few
7 hundred nanograms. But yet one meal is
8 able to bypass the liver and the NDMA get
9 into the bloodstream?

10 A. I don't know that. I
11 haven't read these studies. They weren't
12 what I looked at in looking at NDMA
13 metabolism.

14 Q. If just a couple hundred
15 nanograms can bypass the liver, then, I
16 mean, tens of thousands of nanograms of
17 NDMA would definitely bypass the liver,
18 correct?

19 MS. THOMPSON: Objection to
20 form.

21 THE WITNESS: I can't answer
22 that without looking at these
23 studies.

24 BY MR. VAUGHN:

1 Q. It's a hypothetical. It's
2 an if/then. If a few hundred was able to
3 bypass, then definitely tens of
4 thousands, correct?

5 MS. THOMPSON: Objection to
6 form.

7 THE WITNESS: Well, again,
8 you're asking me to accept the
9 "if." And I have to look at these
10 studies before I would accept
11 that.

12 BY MR. VAUGHN:

13 Q. Because you didn't review
14 all the literature before you formed your
15 opinions in this case or before this
16 deposition, right?

17 MS. THOMPSON: Objection.
18 Form.

19 THE WITNESS: I was not
20 focused on dietary NDMA.

21 BY MR. VAUGHN:

22 Q. Are you going to review
23 these studies after this deposition?

24 A. I could.

1 Q. And if you change your
2 opinions, are you going to notify us?

3 A. If I change my opinions, I
4 would notify you.

5 MS. THOMPSON: You will
6 notify us, and we will notify.

7 THE WITNESS: Well.

8 BY MR. VAUGHN:

9 Q. Doctor, can you explain how
10 you did your dosage conversions around
11 animal to human?

12 A. I just used milligrams per
13 kilogram. And the average typically used
14 weight for a human is 70 kilograms.

15 Q. Based on what authority did
16 you decide that the -- scratch that one
17 second.

18 The average typically used
19 weight for a human is 70 kilograms. What
20 did you base that off of?

21 A. That's been a historical
22 number that you can find in the
23 literature for literally decades.

24 Q. So it's not like a standard

1 of practice in pharmacy and stuff that
2 you would use 70 kg for a human?

3 MS. KAPKE: Object to form.

4 THE WITNESS: Sorry. Not
5 any more standard to pharmacy than
6 it is to any of the other health
7 professions.

8 BY MR. VAUGHN:

9 Q. Including oncology?

10 A. Including oncology,
11 including cardiology, nephrology. That's
12 been in the literature as sort of a
13 standard for a long time, probably longer
14 than what would be accurate today. I
15 think the number today would probably be
16 even bigger.

17 Q. It's important to have that
18 number be accurate, correct?

19 A. In a comparative basis, not
20 necessarily. But you know, it's ballpark
21 enough to make the point.

22 Q. And so you don't know -- you
23 said that cancer research oncologists,
24 they all use 70 kg, right?

1 MS. THOMPSON: Object to
2 form.

3 THE WITNESS: I didn't say
4 that. I said it's been accepted
5 by all branches of the medical and
6 pharmacy and nursing communities
7 when people are sort of talking
8 about what the average human
9 weight is. And that's been around
10 for decades.

11 BY MR. VAUGHN:

12 Q. Did you do any research to
13 make sure that that's the weight that's
14 used when you're dealing with a
15 carcinogen?

16 MS. THOMPSON: Objection.
17 Form.

18 THE WITNESS: No, I did not.

19 BY MR. VAUGHN:

20 Q. You just assumed that you
21 would use the same weight?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: Again, it's

1 for a relative basis.

2 If I were to use 10
3 kilograms less or 10 kilograms
4 more, or 20 kilograms more, it
5 wouldn't change my opinions.

6 BY MR. VAUGHN:

7 Q. Isn't it your opinion that
8 the levels of NDMA present in generic
9 valsartan don't increase the risk of
10 cancer for anyone taking it?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: Could you
14 rephrase that again for me,
15 please?

16 BY MR. VAUGHN:

17 Q. Yeah.

18 Is it your opinion that the
19 levels of NDMA that were present in
20 generic valsartan did not pose an
21 increased risk of cancer formation for
22 anyone that took the drug?

23 A. Yes. That's in my report.

24 Q. If your opinion is on anyone

1 that took the drug, why are you using
2 average human weight?

3 A. For comparative purposes. I
4 guess I could have used, if I had them,
5 the weights of all the people who took
6 the drug. But I didn't have that.

7 Q. I mean, wouldn't
8 approximately half of humans weigh less
9 than the actual weight of a human?

10 A. Yes.

11 Q. If you were so confident in
12 your opinions that the levels of NDMA in
13 valsartan can't cause or increase the
14 risk of human cancer, why didn't you just
15 go with the lowest weight value. Why did
16 you use average?

17 MS. THOMPSON: Objection.

18 Form.

19 THE WITNESS: I don't know
20 what the lowest weight would have
21 been. But had I picked, you know,
22 60 kilograms or 20 or -- I don't
23 know what you mean, because I
24 don't know what that number is.

1 BY MR. VAUGHN:

2 Q. Well, it significantly
3 impacts your calculation, does it not?

4 MS. THOMPSON: Objection.
5 Form.

6 THE WITNESS: No. It really
7 doesn't. If you look at my table,
8 you know, where I use the 70-kilo,
9 and get 7,000 milligrams, as what
10 appeared to be a non-cancerous
11 dose based on a .1 milligram per
12 kilogram in rat studies, whether
13 that number is 6,000 or in the
14 case of someone who's larger,
15 whether that number is 15,000, it
16 doesn't change my opinions.

17 BY MR. VAUGHN:

18 Q. All right. Based on your
19 methodology, if 1 nanogram of NDMA was
20 able to induce cancer in an animal that
21 weighed one kilogram, then based on your
22 calculations, it would take 70 nanograms
23 to induce cancer in a human; is that
24 correct?

1 A. Well, I never calculated
2 that.

3 Q. Well, I know you didn't do
4 this calculation. But the way you're
5 doing your conversion -- and so I'm not
6 trying to represent that one nanogram
7 causes cancer in animals. I'm just using
8 these numbers for simplicity's sake
9 because I want to understand your
10 methodology and how you came to these
11 numbers.

12 Does that make sense?

13 A. Yeah, we can just use the
14 numbers and use them. We don't have to
15 use something other than the numbers.

16 Q. Well, I need the math to be
17 a lot easier, is why I'm doing it this
18 way.

19 A. Okay. This is pretty easy.

20 Q. So you're just taking
21 whatever the nanograms per kilogram are
22 and you're timesing them by 70, correct?

23 A. And they're actually
24 micrograms and/or milligrams, and not in

1 the nanogram range.

2 Q. Would you be more
3 comfortable if I gave my hypothetical in
4 micrograms instead of nanograms? Would
5 that make it easier for you?

6 A. Well, like I said, we can
7 just use the numbers. They're not that
8 complicated. .1 --

9 Q. I'm allowed to ask you
10 hypotheticals. And if I use basic
11 numbers it's a lot easier for the jury to
12 understand what your methodology is.

13 So if 1 microgram of NDMA
14 was able to induce cancer in an animal
15 that weighed 1 kilogram, based on your
16 calculations, it would take 70 micrograms
17 to induce cancer in a human; is that
18 correct?

19 MS. THOMPSON: Objection.
20 Form.

21 THE WITNESS: Again, if that
22 were the case, which isn't the
23 case.

24 BY MR. VAUGHN:

1 Q. But the way I did my math
2 was how you did your methodology,
3 correct?

4 A. Well, multiplying by 70,
5 yes.

6 Q. Okay. And so for every kg,
7 you added 100 percent of that base dose,
8 correct?

9 A. For a dose that did not
10 cause cancer in rats, that in a few
11 studies was fairly consistent
12 around .1 milligrams per kilogram, I
13 extrapolated that to the average weight
14 of a human adult, which is 70 kilograms.
15 So 70 times the .1 gave 7 milligrams,
16 which is 7,000 micrograms.

17 Q. Thank you, Doctor.

18 And so, if an animal weighs
19 70 times as much as another animal, based
20 on your methodology, it's going to take
21 70 times the amount of NDMA to have the
22 same impact on that animal, correct?

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: I don't think
2 that's what I'm saying here.

3 BY MR. VAUGHN:

4 Q. Can you explain to me what
5 you're saying then?

6 A. Well, you again, reverted
7 from the dose I said that doesn't cause
8 cancer to a dose that does cause cancer,
9 and I'm not claiming to know what that
10 is.

11 Q. Okay. Let's set aside
12 causing cancer. One nanogram per
13 kilogram would be the same as 70
14 nanograms for 70 kilograms.

15 That's what your math came
16 out to be, right?

17 A. Correct. That's the math.

18 Q. Okay. And is that known as
19 linear extrapolation?

20 MS. THOMPSON: Objection to
21 form.

22 THE WITNESS: I don't know
23 if that's the term that's used.
24 But that would describe it

1 accurately, I think.

2 BY MR. VAUGHN:

3 Q. So it's like a one to one
4 ratio, right? Like, for every kg, you
5 add one part of the base, right?

6 A. Yeah. As long as it's
7 reported in kilograms.

8 Q. And what was your basis that
9 that one-to-one ratio was appropriate to
10 use for NDMA?

11 A. It's just the best that we
12 have. We don't have any other method of
13 conversion based on some other
14 physiologic factor. It's how the animals
15 were dosed. They were dosed in
16 milligrams per kilogram.

17 Q. But you have no basis for
18 why that's appropriate to extrapolate
19 them to humans based on weight?

20 A. Well, as I've already said,
21 we are not sure that extrapolating these
22 animal data to humans is accurate and the
23 right thing to do to begin with.

24 So we have some missing

1 parts. We've got the milligram per
2 kilogram dose in the animals, what dose
3 didn't cause cancer, we have the weight,
4 the average weight of a human adult, and
5 then we have how much microgram
6 quantities were in the valsartan product.

7 So there's that missing link
8 connection that is an assumption that is
9 being made.

10 Q. Okay. Let's set humans
11 aside then.

12 If two different animal
13 species, each weighed one kilogram, you
14 would expect the exact same amount of
15 NDMA to be necessary to induce cancer in
16 those animals, correct?

17 A. No.

18 Q. Why?

19 A. Different amounts of 2E1.

20 Q. Does a rat and a mouse have
21 different amounts of 2E1?

22 A. I believe they do. I know
23 for sure a rat and a dog do and a rat and
24 a monkey does and a rat and a pig does.

1 Q. But you don't know if a rat
2 and a mouse have different amounts?

3 A. I don't recall seeing that.
4 And the reason I do know about the
5 monkeys and the pigs and the beagle dogs,
6 is because there were studies that I
7 reviewed that were in that area.

8 Q. And so you didn't consider
9 the amount of 2E1 in mice when forming
10 your opinions in this case?

11 A. No, I did not.

12 Q. Based on what you just said
13 about the 2E1, assuming that they have
14 comparable amounts of 2E1. An animal
15 that weighs, let's say, 12 times as much
16 as another animal, you would expect it to
17 take 12 times the amount of NDMA to have
18 the same impact, correct?

19 A. Well, I'm saying the dose
20 would be. I am not saying what the
21 impact would be. There's other parts to
22 the question about causing cancer. And
23 it has to do with the amount of 2E1 in
24 the different organs and what the dose is

1 and whether you exceed first-pass
2 metabolism, and do you give it IV or PO.

3 There's all these moving
4 parts to the puzzle to even get close to
5 having an apples-to-apples kind of
6 comparison.

7 Q. Well, assuming that you're
8 giving it the same route, you know,
9 giving it orally for each of them.

10 A. Right. But again, they have
11 different amounts of 2E1.

12 Q. I said assuming that they
13 had comparable amounts of 2E1. I mean,
14 you're assuming that human and rats have
15 comparable amounts, right?

16 A. Well, that's been
17 demonstrated. And I can't say it across
18 all species.

19 Q. You don't know if mice have
20 anything similar?

21 A. I just didn't look at that,
22 no.

23 Q. You listed, "2018 M7(R1)
24 Assessment and Control of DNA" --

1 reactivity -- "Reactive Impurities in
2 Pharmaceuticals to Limit Potential
3 Carcinogenic Risk: A Guidance For the
4 Industry."

5 Did you read that entire
6 document?

7 A. I did.

8 Q. And did you consider the
9 2018 guidance for the industry in forming
10 your opinions?

11 A. I considered them. But they
12 didn't have an impact on my opinions.

13 Q. Do you recall disagreeing
14 with anything from the 2018 guidance for
15 industry?

16 A. It doesn't mean that I
17 disagreed with them. It just means that
18 they didn't have an impact on the
19 conclusions that I drew based on NDMA
20 metabolism relative to the amounts of
21 NDMA found in the valsartan products.

22 Q. But what I was asking is do
23 you recall disagreeing with anything in
24 the guidance?

1 A. I don't recall being in any
2 position to disagree with it. I just was
3 familiar with it.

4 Q. And would you follow a
5 guidance document like that?

6 MS. THOMPSON: Objection.
7 Form.

8 THE WITNESS: I read the
9 guidance document. I don't know
10 what you mean by follow.

11 MR. VAUGHN: Tyler, you can
12 go ahead and pull that up for me.
13 The 2018 M7(R1).

14 (Document marked for
15 identification as Exhibit
16 Bottorff-5.)

17 BY MR. VAUGHN:

18 Q. Guidance for industry.
19 Who's the industry that this is supposed
20 to guide?

21 A. Pharmaceutical industry.

22 Q. That's who you represent,
23 correct?

24 A. Correct.

1 Q. And at the bottom here, what
2 agencies are responsible for this
3 guidance document?

4 A. HHS, FDA, the CDER, CBER,
5 which are branches of the FDA.

6 Q. So the U.S. Department of
7 Health And and Human Services, the Food &
8 Drug Administration, the Center for Drug
9 Evaluation & Research, and the Center For
10 Biologic Evaluation & Research; is that
11 correct?

12 A. Yes. Just to clarify, CDER
13 and CBER are branches of the FDA, and the
14 FDA is a branch of the Health & Human
15 Services.

16 Q. Okay. So this guidance
17 document is basically put out by the U.S.
18 Department of Health & Human Services?

19 A. Under the auspices of the
20 FDA, and it's two specific branches that
21 did the work.

22 Q. And what year was this put
23 out?

24 A. 2018.

1 Q. And when did the industry --
2 or not the industry. Scratch that.

3 When did the FDA
4 approximately learn about the valsartan
5 contamination with NDMA?

6 MS. THOMPSON: Objection.

7 Form.

8 THE WITNESS: I think it was
9 in July of 2018 that they
10 announced. I can't remember the
11 exact date. But it was in 2018.

12 MR. VAUGHN: Go to Page 39,
13 Tyler. Actually, one second. One
14 second. Page 24. Can you go back
15 two pages actually, Tyler, for me.
16 I'm sorry. I got my PDF stuff
17 wrong. That works. All right.
18 Got it. Sorry. I'm having a hard
19 time seeing it. Go -- no, no.

20 BY MR. VAUGHN:

21 Q. Do you see here what kg body
22 weight they are using?

23 A. 50.

24 Q. And you used 70, correct?

1 A. Correct.

2 MS. THOMPSON: I think I'm
3 in the wrong document. Is this in
4 the shared file?

5 MR. VAUGHN: I mean, it's in
6 his materials considered that you
7 gave us.

8 MS. THOMPSON: I understand.
9 I'm just trying to make sure that
10 I'm pulling up the right one
11 because the last exhibit that I
12 have in here is Exhibit 5, which
13 looks like it's the guidance
14 document.

15 MR. VAUGHN: The first page
16 says "Guidance for Industry.
17 M7(R1)." It's March 2018.

18 BY MR. VAUGHN:

19 Q. So would you agree with me,
20 Doctor, when the FDA is doing their
21 calculations on carcinogens, they use a
22 50 kg weight, not 70 kg rate?

23 MS. THOMPSON: Objection to
24 form.

1 THE WITNESS: They did use
2 50.

3 BY MR. VAUGHN:

4 Q. And do you know if they
5 always use 50 when it's a carcinogen?

6 A. I do not know that. I think
7 they -- I don't know if it's here or
8 somewhere else that they explained their
9 use of the 50 kilos, so they would be in
10 their calculations on the
11 ultra-conservative side.

12 Q. And why would they want to
13 be on the more conservative side?

14 A. Because they're a regulatory
15 agency. I don't know.

16 Q. Do you think it might have
17 anything to do with not wanting people to
18 get cancer?

19 MS. THOMPSON: Object to
20 form.

21 THE WITNESS: I'm sure they
22 don't want people to get cancer.

23 BY MR. VAUGHN:

24 Q. And so setting that lower kg

1 rate gives them a little bit more
2 assurance, right?

3 MS. THOMPSON: Objection.
4 Form.

5 THE WITNESS: Not
6 necessarily, but that's what they
7 chose to do.

8 BY MR. VAUGHN:

9 Q. What do you mean not
10 necessarily? Isn't timesing something by
11 50 going to result in a lower number than
12 timesing something by 70?

13 MS. THOMPSON: Objection to
14 form.

15 THE WITNESS: Every time.

16 MR. VAUGHN: All right.

17 Sorry. I got off. I don't know
18 where I was at.

19 BY MR. VAUGHN:

20 Q. Doctor, you also listed the
21 FDA's February 2021 "Control of
22 Nitrosamine Impurities in Human Drugs:
23 Guidance For Industry" on your list of
24 your materials considered.

1 Do you recall reading that
2 document?

3 A. I do.

4 Q. And did you read that entire
5 document?

6 A. I probably scanned that one
7 in case there was something different
8 than what I had seen before. I don't --
9 I don't remember specifically if I read
10 the entire word for word.

11 Q. You don't recall if FDA's
12 guidance document lays out a different
13 methodology than the one that you used in
14 forming your opinions?

15 A. Well, I believe the document
16 that you just have up there now used a
17 different methodology than I used.

18 Q. And why did you decide to
19 use a different methodology than the FDA?

20 A. They have a different focus.

21 Q. Is their focus more on
22 patient health and your focus is more on
23 defending a pharmaceutical company?

24 MS. THOMPSON: Objection.

1 Form.

2 THE WITNESS: Well, my focus
3 was on the science behind looking
4 at a non-cancerous dose as opposed
5 to trying to extrapolate something
6 over 70 years in a 50-kilogram
7 person, which I think is their
8 more regulatory approach. I tried
9 to look at the science and
10 conclude what was available.

11 BY MR. VAUGHN:

12 Q. You didn't even look into
13 like, mutagenicity and stuff, did you?

14 MS. THOMPSON: Object to
15 form.

16 THE WITNESS: I'm not sure
17 what you're asking.

18 BY MR. VAUGHN:

19 Q. That's fine. We'll get into
20 it more.

21 MR. VAUGHN: Tyler, can you
22 pull up the 2021 guidance for
23 industry.

24 And what exhibit number is

1 this going to be, Tyler? I'm
2 sorry. Is it five?

3 TRIAL TECH: This is going
4 to be six.

5 MR. VAUGHN: Six. Thank
6 you.

7 (Document marked for
8 identification as Exhibit
9 Bottorff-6.)

10 BY MR. VAUGHN:

11 Q. I'm trying to stay organized
12 as we go. Can we go to -- this is what I
13 want to go to 24.

14 MR. VAUGHN: Can we go to 24
15 now, Tyler. Sorry about that.

16 BY MR. VAUGHN:

17 Q. All right. If we go --

18 MR. VAUGHN: Sorry. You
19 were at the page I wanted.

20 TRIAL TECH: Okay. I was
21 going to say, it doesn't look like
22 there's a Page 24. But this is
23 the last one.

24 MR. VAUGHN: The last one.

1 That's what I meant. Of the
2 document, Page 24 -- or of the
3 PDF.

4 BY MR. VAUGHN:

5 Q. All right. And, Doctor, if
6 we go to Line 39. Do you see where the
7 FDA in this 2021 guidance to the industry
8 is still recommending that 50 kg be
9 utilized when doing conversions to
10 humans?

11 Doctor?

12 MR. REEFER: Excuse me,
13 Brett. Can you hear me?

14 MR. VAUGHN: I can. Can you
15 guys not hear me?

16 MR. REEFER: We're having
17 some technical difficulties in the
18 room. I apologize for
19 interjecting. This is Jason from
20 the Pietragallo firm.

21 MR. VAUGHN: No problem.
22 You guys -- is it fixed now?

23 MS. THOMPSON: No. We're on
24 this computer only. So I'm trying

1 to shut down and redo my
2 connection since I control the
3 mic.

4 THE VIDEOGRAPHER: Should we
5 go off the record?

6 MR. VAUGHN: Go off the
7 record. Yeah.

8 THE VIDEOGRAPHER: The time
9 right now is 2:52 p.m. We're off
10 the record.

11 (Short break.)

12 THE VIDEOGRAPHER: The time
13 right now is 2:57 p.m. We're back
14 on the record.

15 BY MR. VAUGHN:

16 Q. Doctor, is the amount of
17 P450-2E1 going to impact how much NDMA it
18 takes to kill an animal?

19 A. Not necessarily.

20 Q. What do you mean by not
21 necessarily?

22 A. Well, you can give a massive
23 IV dose that goes -- that totally
24 disrupts liver function and causes

1 massive bleeding which has been done and
2 that has nothing to do with 2E1.

3 Q. Line 39, I don't know if we
4 got the question in before you guys
5 disconnected earlier. The FDA here in
6 2021 is still recommending to use 50 kg
7 as the body weight, correct?

8 MS. THOMPSON: Objection.
9 Form.

10 THE WITNESS: I don't think
11 they are recommending that I or
12 anyone else use 50 kilograms.
13 It's what they did in their
14 calculation.

15 BY MR. VAUGHN:

16 Q. And they're still doing that
17 calculation in 2021 with 50 kilograms,
18 correct?

19 A. Correct.

20 Q. And so, on that example we
21 gave earlier, that one nanogram per
22 kilogram for human, with your
23 methodology, you would come out at 70
24 nanograms. Based on the FDA's

1 methodology, it would be 50-nanograms,
2 correct?

3 A. Yeah. And we can apply that
4 to my calculations where the .1 milligram
5 per kilogram dose that doesn't appear to
6 cause cancer in rats, we can multiply it
7 by 50 and I get 5,000 milligrams instead
8 of 7,000 milligrams. And that wouldn't
9 change my conclusions at all.

10 Q. Down at the -- towards the
11 bottom, Line 52. It's talking about TD50
12 values. Do you know what a TD50 value
13 is?

14 A. I do.

15 Q. Can you explain to the jury
16 what a TD50 value?

17 A. It's the dose given to the
18 animal that you've decided to give it to
19 that kills half of the animals. It's
20 sort of like the lethal 50 dose.
21 Actually it's -- in this case, it's the
22 tumor dose. It gives half the animals
23 tumors.

24 Q. The amount that's needed per

1 kg is half as much for a rat as it is for
2 a mouse, isn't it?

3 A. Yes.

4 Q. And you don't know if that's
5 because of P450-2E1 or if it's because as
6 you increase weight it's not proportional
7 of the dose that you need to give the
8 animal, correct?

9 MS. THOMPSON: Objection.
10 Form.

11 THE WITNESS: It's correct
12 that I don't know what the reason
13 for that is. It could be that
14 the -- that the rat are more
15 resistant to getting tumors than
16 the mice.

17 I mean, there is a number of
18 reasons why that might be the
19 case.

20 BY MR. VAUGHN:

21 Q. You never investigated what
22 that reason is in forming your opinions,
23 did you?

24 A. I did not.

1 Q. And if the reason is because
2 it's not a linear relationship when you
3 increase weight to dose, then that would
4 significantly impact your opinions,
5 wouldn't it?

6 MS. THOMPSON: Objection.
7 Form.

8 THE WITNESS: No. In fact,
9 the FDA used the milligram per
10 kilogram in their calculations. I
11 mean, so they're comfortable using
12 milligrams per kilogram.

13 BY MR. VAUGHN:

14 Q. The FDA did in this example.
15 But what I'm saying is if the rat is
16 increasing in weight, but only needs half
17 as much per kilogram, then that's more
18 like a 50 percent ratio, right, as
19 opposed to the 100 percent ratio?

20 MS. THOMPSON: Objection to
21 form.

22 THE WITNESS: This means
23 that it takes less drug by about
24 half in the rat versus the mouse

1 to cause a tumor in half of them.

2 BY MR. VAUGHN:

3 Q. And if that held true as the
4 weight kept going up all the way to a
5 human and we use the FDA's 50 kg, then
6 that would only be -- half of 50 is 25,
7 right? So you'd multiply it by 25
8 instead, if this held true for humans,
9 correct?

10 A. Again, we're not applying
11 the mouse data to the humans.

12 Q. You're not applying the
13 mouse data to the human?

14 A. And nor did any of the other
15 studies that I looked at.

16 Q. And you didn't consider the
17 mouse data?

18 MS. THOMPSON: Objection to
19 form.

20 THE WITNESS: I did not.
21 Sorry.

22 BY MR. VAUGHN:

23 Q. I don't know if -- did you
24 answer that? I don't see it on -- oh,

1 there it is. My internet is now
2 unstable. Are you able to hear me?

3 A. I think I said correct.

4 Q. You did. I guess my
5 internet was having -- was going a little
6 slow there.

7 So there is a citation for
8 this, isn't there? Citation Number 3.
9 And what is that citation?

10 A. In the document?

11 Q. Yeah.

12 A. It's this carcinogenicity
13 potency database for NDMA.

14 Q. And who published that
15 database?

16 A. I'm not sure publishes it.
17 But this is a reference to the National
18 Library of Medicine collection of those
19 databases.

20 Q. Is that what the NLM part of
21 that -- and then it has a ".NIH"; is
22 that -- what's the NIH part there?

23 A. I guess that's indicating
24 that the National Library of Medicine is

1 part of the NIH.

2 Q. And that's the National
3 Institute of Health, correct?

4 A. Correct.

5 Q. And that's what we were
6 talking about earlier, the National
7 Institute of Health that continues to
8 fund Dr. Panigrahy -- sorry. Scratch
9 that.

10 That's the same National
11 Institute of Health that we talked about
12 earlier that continues to fund
13 Dr. Panigrahy's cancer research, correct?

14 A. Correct.

15 MS. THOMPSON: Object to
16 form.

17 BY MR. VAUGHN:

18 Q. It's a hard name sometimes.
19 Doctor, do you know what the
20 average rate -- I can't talk anymore.

21 Doctor, do you know what the
22 average weight of a rat was that was
23 studied with NDMA?

24 A. I looked at that, because in

1 some cases it wasn't so clear what that
2 number was. And in other cases it was
3 more clear.

4 Most of these rats were in
5 the 300, 350, 400, 450 range, depending
6 on their age and whether they were male
7 or female.

8 Q. And the mice, did you
9 calculate their average weight too?

10 A. I did not.

11 Q. You didn't calculate their
12 weight at .025 kg?

13 A. I did not.

14 MR. VAUGHN: Go to his
15 expert report. Go to Page 44.

16 BY MR. VAUGHN:

17 Q. On Line 728, where you note
18 the rough estimate of 25 grams or 0.025
19 kg for the mice, what did you base that
20 off of? Or do you not recall putting
21 that into your expert report?

22 A. No, I recall. This was one
23 of the mice studies that I looked at, and
24 I don't believe in the paper they

1 actually reported the weights.

2 So to do my calculation, I
3 had to go to the laboratory animal place
4 where you go buy them and look at that
5 specific strain and then look at the
6 weights that they give.

7 Q. Did you not look at any
8 other NDMA studies in mice to see what
9 weights they were in those studies?

10 A. No. I don't recall any
11 other one.

12 Q. Why didn't -- why didn't you
13 do that?

14 A. As I did my search and
15 started looking for articles that had
16 some kind of dose-response relationship
17 that would indicate a non-cancerous dose,
18 the vast majority of that data were in
19 rats. And so I used predominately rat
20 data.

21 Q. Did you give more weight to
22 the rat data just because more studies
23 have been done in rats?

24 A. No. As I said earlier, I

1 gave more weight because many of these
2 researchers talk about how the rat liver
3 metabolism is the closest to human liver
4 metabolism, which is why I think there's
5 way more rat studies in this area than
6 there is any other species.

7 Q. So you wouldn't exclude any
8 animal data just because it wasn't a rat,
9 right?

10 A. It depends on the data are
11 and what they found and how they got it.

12 Q. So, like, if the data showed
13 that it increased the risk of cancer for
14 another animal, you wouldn't discount
15 that animal just because it wasn't a rat,
16 right?

17 A. No, I wouldn't discount
18 that. But again, I was looking for doses
19 that didn't cause cancer, not doses that
20 did. And many of these are on the doses
21 given to cause cancer.

22 Q. But you wouldn't exclude an
23 animal just because it wasn't a rat?

24 A. I wouldn't exclude looking

1 at the study. But I might exclude
2 pharmacokinetic data or something else
3 that is less applicable to what my
4 question was.

5 Q. What about just not
6 mentioning it in your study, like the
7 animal. Like, you only focus on the rat
8 when the study looked at rats and another
9 animal?

10 A. I think it was appropriate
11 to focus on the rat because that's the
12 animal that best approximates metabolism,
13 which is what the focus of my report was.

14 Q. Right. You don't even know
15 what the metabolism is in a mouse. So
16 how do you know that the rat is the
17 closest to a human?

18 MS. THOMPSON: Objection.
19 Form.

20 THE WITNESS: Because of all
21 the studies that I looked at.

22 BY MR. VAUGHN:

23 Q. What's a hamster? How close
24 is that to a human?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: I don't know
4 for sure. I know studies have
5 been done. But not that many.

6 MR. VAUGHN: Can we go to
7 Page 46 of your expert report now.
8 And can we go to Line 766.

9 BY MR. VAUGHN:

10 Q. And can you read the
11 sentence for the jury that starts with
12 "rats"?

13 A. "Rats and hamsters were
14 studied, but given the preponderance of
15 rat studies, only the rat data are shown
16 here."

17 Q. Is this consistent with what
18 you just testified to?

19 A. Yes.

20 Q. How?

21 A. That the preponderance of
22 evidence comes from rat data.

23 Q. And so you discounted the
24 hamster data because it wasn't a rat,

1 right?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I did not
5 include it because the rats are
6 the closest and I wanted to look
7 at as many rat studies as I could.

8 BY MR. VAUGHN:

9 Q. And again, how can you say
10 that rats are closer to humans than
11 hamsters if you don't know what hamsters'
12 metabolism is like?

13 A. When the researchers in my
14 research say rats are closest, I believe
15 them.

16 Q. So you would defer to
17 someone else on that, correct?

18 MS. THOMPSON: Objection.

19 Form.

20 THE WITNESS: For the people
21 who do animal studies in this
22 area, yes, I would.

23 BY MR. VAUGHN:

24 Q. So, like, a cancer

1 researcher that focuses on animal
2 studies, you would defer to that cancer
3 researcher, correct?

4 A. I would refer to the study,
5 regardless of who the researcher was.

6 Q. Defer?

7 A. I would defer to their
8 conclusion that they chose that animal
9 for a reason.

10 Q. And so if a cancer
11 researcher with a specialty in animal
12 studies says that some other animal
13 besides a rat is closest to a human in
14 how they metabolize NDMA, you would defer
15 to that cancer researcher, correct?

16 MS. THOMPSON: Objection to
17 form.

18 THE WITNESS: I would look
19 at that, yes.

20 BY MR. VAUGHN:

21 Q. Would you defer to them?

22 MS. THOMPSON: Objection.

23 Form.

24 THE WITNESS: Again, if it's

1 one study, no. If it's, as in
2 this case, dozens and dozens of
3 studies that said that about the
4 rat, then I would defer to the rat
5 studies.

6 BY MR. VAUGHN:

7 Q. But again, you don't know
8 about how other animals compare to humans
9 when it comes to their metabolism of
10 NDMA, correct?

11 A. Well, that's not true. I
12 have looked at that.

13 Q. Okay. Hamsters, did you
14 look at hamsters?

15 A. I read the study. But I
16 don't recall the hamster data.

17 Q. Okay. But -- sorry?

18 A. That's okay.

19 As I previously testified, I
20 did look at the swine data. I did look
21 at the beagle data. I did look at the
22 monkey data.

23 Q. But not the hamster or the
24 mouse?

1 A. Well, I did report on a
2 mouse study. I just didn't report on a
3 hamster study.

4 Q. But you didn't look into
5 either a mouse or a hamster as it relates
6 to metabolism of NDMA, correct?

7 A. I did one mouse study. We
8 just looked at it.

9 Q. But that had to do with how
10 the mouse metabolizes NDMA?

11 A. I think it had to do with
12 alcohol and the effects of NDMA.

13 Q. And what impact does alcohol
14 have on NDMA?

15 A. Go back to the study --
16 which one was it? Will someone refresh
17 my memory where it was.

18 MS. THOMPSON: Page 44.

19 THE WITNESS: Page --

20 MS. THOMPSON: 44.

21 THE WITNESS: 44?

22 Oh, the Gricute.

23 BY MR. VAUGHN:

24 Q. Where in that paragraph that

1 you're talking about on Page 44 that you
2 discuss the metabolism of NDMA in mice?

3 A. I don't. I'd have to pull
4 the study to see why I only put this
5 amount of data in. But it was trying to
6 get at what was the dose that was being
7 studied.

8 And again, my focus for this
9 report was to try to find studies that
10 gave doses that did not produce cancer.

11 And they gave such a large
12 dose, that it didn't give me evidence
13 with which to reach my conclusions.

14 Q. So in forming your opinions,
15 you only considered data or studies that
16 did not cause cancer, you didn't consider
17 the ones that did cause cancer, correct?

18 MS. THOMPSON: Objection.

19 Form.

20 THE WITNESS: Untrue,
21 because many of these studies also
22 caused cancer. But what I was
23 interested in is if they had dose
24 regimens small enough to allow me

1 to evaluate a noncancer-causing
2 dose and what that dose was and
3 how it correlated to the amount of
4 NDMA in the valsartan products.

5 BY MR. VAUGHN:

6 Q. Did you try and look for any
7 literature on low doses causing cancer in
8 animals?

9 MS. THOMPSON: Objection.
10 Form.

11 THE WITNESS: I think, in a
12 way that's what I just said, is I
13 looked for studies that had enough
14 of a low dose of the dosage range
15 on the low end, to have a low
16 enough dose to not cause cancer,
17 if that existed. And if it didn't
18 exist, it didn't. But it did.

19 BY MR. VAUGHN:

20 Q. Were you only looking for
21 ones where it did not cause cancer?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: If there were

1 low dose studies that did cause
2 cancer, I looked at them and I
3 included them. But I was focusing
4 on low dose studies that had an
5 arm that didn't cause cancer so I
6 could try to find how that low
7 dose noncancer-causing dose
8 related to NDMA in valsartan.

9 BY MR. VAUGHN:

10 Q. So any low dose studies that
11 did cause cancer would be contained in
12 the body of your expert report, correct?

13 A. Well --

14 Q. Let me rephrase that. So
15 any low dose studies that did cause
16 cancer that you relied on in forming your
17 opinions in this case would be contained
18 in the body of your expert report,
19 correct?

20 A. I believe so, yes.

21 Q. I see a 1978 document from
22 the WHO on nitrosamines on your materials
23 considered list.

24 What is the WHO?

1 A. The World Health
2 Organization.

3 Q. Is that a reputable
4 organization?

5 A. Yes.

6 Q. Is that an authoritative
7 organization?

8 A. Yes.

9 MR. VAUGHN: Tyler, do you
10 mind pulling the -- yeah, 2002
11 WHO.

12 (Document Marked for
13 identification as Exhibit
14 Bottorff-7.)

15 BY MR. VAUGHN:

16 Q. Did you review anything
17 after the 1978 one? I don't see this
18 2002 one on your materials considered.

19 A. I have one that's dated
20 2002. So I have looked at this.

21 Q. Oh, good. Is it included on
22 your materials considered?

23 A. I don't know. But I
24 actually looked at this, I don't know, a

1 couple days ago. So I know I've seen it.

2 Q. Did you consider it when
3 forming your opinions in this case?

4 A. We're looking for it. I
5 don't know.

6 Q. All right. 2002 is a lot
7 more recent than 1978, isn't it?

8 A. Yes.

9 Q. A lot has changed, you know,
10 from 1978 to 2002 in science. Wouldn't
11 you agree?

12 MS. THOMPSON: I'm giving
13 him the list of materials
14 considered.

15 BY MR. VAUGHN:

16 Q. I could have missed it. So
17 please double-check and let me know if
18 you included that on your materials
19 considered.

20 A. Yeah, I have the article. I
21 know I looked at it. I just don't see it
22 at this point on the materials
23 considered.

24 Q. Do you recall anything in

1 this document that is counter to your
2 methodology?

3 A. Not that I recall.

4 Q. Would you want your
5 methodology to be counter to what the WHO
6 recommends?

7 MS. THOMPSON: Objection.
8 Form.

9 THE WITNESS: It depends on
10 what they're recommending. So I
11 don't know -- I don't know how to
12 answer that.

13 BY MR. VAUGHN:

14 Q. It's fine. I'll be a little
15 more specific for you.

16 MR. VAUGHN: Tyler, do you
17 mind taking us to PDF Page 27. I
18 think it's 23 on the bottom of the
19 document though.

20 BY MR. VAUGHN:

21 Q. I guess before we do that,
22 this n-nitroso -- how do you say that?

23 A. N-nitrosodimethylamine.

24 Q. What is that?

1 A. That's NDMA.

2 Q. So this document is specific
3 to NDMA?

4 A. Yeah. And I did find this
5 in my -- in my documents that I reviewed.

6 Q. It's on your materials
7 considered list?

8 A. Very top of Page 5.

9 Q. Okay. See, I do -- oh, but
10 WHO is further in there. That's why I
11 missed it. Thank you for pointing that
12 out.

13 A. No problem. I know I had
14 seen it.

15 Q. Appreciate it.

16 MR. VAUGHN: So yeah, now,
17 can we go to Page 27 of the PDF,
18 Tyler.

19 BY MR. VAUGHN:

20 Q. And then under dose-response
21 analysis, can you read that entire second
22 paragraph for the jury, Doctor?

23 A. "Scaling for variations in
24 the ratios of surface area to body weight

1 between rodent species and humans was not
2 considered appropriate for the measures
3 of exposure response developed on the
4 basis of experimental data in animals,
5 since it's highly probable that the
6 carcinogenicity of NDMA is mediated
7 primarily through the generation of an
8 active metabolite."

9 Q. What do you understand that
10 to mean?

11 A. That means that they chose
12 not to use body surface area, which you
13 use body weight when you calculate body
14 surface area. So they're saying they
15 chose not to use body surface area.

16 Q. So they didn't scale between
17 species to humans?

18 A. Not using body surface area.

19 Q. How did they recommend
20 scaling?

21 A. Well, this doesn't say what
22 they recommended for that.

23 Q. And what's the reason they
24 are saying not to scale based on surface

1 area to body weight?

2 A. Again, I'm not sure how they
3 derived their reason. But the reason
4 they list is mediation through the active
5 metabolite generation.

6 Q. And what active metabolite
7 is that?

8 A. The methyldiazonium ion
9 mediated by 2E1, which we previously
10 talked about the rat model being a good
11 approximation of humans for that.

12 Q. Were you aware that you
13 shouldn't be using surface area to body
14 weight conversions with NDMA?

15 A. I don't recall specifically
16 that comment. But in all these studies,
17 they've used body weight. So that's
18 almost like saying that it's the accepted
19 way to do that, instead of body surface
20 area.

21 Q. Your opinion is it's almost
22 like saying it's accepted to do it the
23 way you did?

24 A. I would say that if I did it

1 using body surface area, I would have
2 been wrong in their opinion.

3 Q. This active metabolite, is
4 that a genotoxin?

5 A. That is the genotoxin.

6 Q. So is it because it is a
7 genotoxin they're saying not to do the
8 scaling?

9 MS. THOMPSON: Objection to
10 form.

11 THE WITNESS: Not to my
12 knowledge.

13 BY MR. VAUGHN:

14 Q. It says "since it's
15 highly probable". Isn't "since" kind of
16 like "because", this is the reason we're
17 telling you not to do it?

18 MS. THOMPSON: Object to the
19 form.

20 THE WITNESS: I think so.
21 But it's -- I think you could
22 argue it's metabolism, not the
23 genotoxicity that makes that
24 statement.

1 BY MR. VAUGHN:

2 Q. What do you derive that from
3 in this paragraph?

4 A. Because they don't say we
5 recommend this because it's a genotoxin.
6 They recommend it because of the active
7 metabolite pathway.

8 Q. If it was recommended
9 because it was a genotoxin, would that
10 change the way you did your methodology?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: Yeah,
14 possibly. But that's not what
15 they are saying.

16 BY MR. VAUGHN:

17 Q. Okay. And you've never
18 worked with a genotoxin prior to this
19 litigation, correct?

20 MS. THOMPSON: Objection.
21 Form sorry.

22 THE WITNESS: Sorry. What
23 do you mean by work?

24 BY MR. VAUGHN:

1 Q. Did you not testify earlier
2 that you have not had experience with
3 genotoxins prior to this litigation?

4 A. I don't think that's exactly
5 how I worded it because I think you did
6 use the word "work with," and I wanted
7 you to define it.

8 Q. And I said, you know,
9 anything. I tossed some examples and I
10 said in any way. And you said no. I
11 mean, can you think of one now?

12 A. No, I said that I had looked
13 at Actos and its genotoxicity. And that
14 I've taken care of hundreds of patients
15 who were cardiac transplant patients that
16 were on immunosuppressive drugs that have
17 the potential to be genotoxic. So it's
18 not a foreign concept to me at all.

19 Q. How much immunosuppression
20 is necessary to be genotoxic?

21 A. I'm not sure. It's not how
22 those drugs are dosed. The
23 immunosuppressive is dosed to prevent the
24 more problem at hand, which is the organ

1 transplant. So they're not dosed based
2 on their genotoxic potential. It's an
3 unwanted side effect if it were to occur.

4 Q. Are you aware if NDMA is an
5 immunosuppressant?

6 A. I'm not aware of that. I
7 focused on its metabolism.

8 Q. And so you didn't consider
9 if NDMA was an immunosuppressant when
10 forming your opinions?

11 A. No. I did not consider
12 that.

13 Q. Right. Immunosuppressant
14 itself can cause cancer, correct?

15 MS. THOMPSON: Object to
16 form.

17 THE WITNESS: I mean, I
18 think that's a blanket yes/no
19 statement, and I think it's
20 probably a lot more complicated
21 than that.

22 BY MR. VAUGHN:

23 Q. But you didn't evaluate any
24 other things that you would need to in

1 forming your opinions, right?

2 MS. THOMPSON: Objection.

3 Form.

4 THE WITNESS: I didn't
5 evaluate immunosuppression as part
6 of my opinions.

7 BY MR. VAUGHN:

8 Q. You didn't even consider
9 immunosuppression, did you?

10 MS. THOMPSON: Objection to
11 form. Asked and answered.

12 THE WITNESS: I did not.
13 Metabolism is what I focused on.

14 MR. VAUGHN: How long have
15 we been going in this section?

16 Have we been on the record a
17 little bit.

18 THE VIDEOGRAPHER:
19 28 minutes.

20 MR. VAUGHN: Oh, yeah, we
21 had that break earlier.

22 Do you need a break, Doctor,
23 or are you good.

24 THE WITNESS: I'm good.

1 MR. VAUGHN: Anyone else?

2 MS. THOMPSON: No.

3 MR. VAUGHN: All right.

4 Tyler, if we can go back to his
5 expert report. And let's look at
6 Page 57 this time.

7 BY MR. VAUGHN:

8 Q. Doctor, can you read aloud
9 the first two sentences of this page?

10 A. "Notably, in Dr. Panigrahy's
11 report on Page 31, he states that only a
12 single dose of NDMA is required to cause
13 and initiate cancer in multiple animal
14 species; however, Dr. Panigrahy did not
15 cite any literature in support of this
16 assertion. Based on my experience and my
17 review of the literature, I do not agree
18 with Dr. Panigrahy's blanket assertion."

19 Q. Dr. Panigrahy, that's the
20 cancer researcher that we've been talking
21 a lot about that the NIH funds, right?

22 A. Right.

23 Q. And you don't agree with him
24 that a single dose of NDMA is capable of

1 inducing cancer, correct?

2 A. I think what I'm stating
3 here is I don't agree with that statement
4 without having a reference to it.

5 Q. And did you review all the
6 literature at the end of Dr. Panigrahy's
7 expert report?

8 MS. THOMPSON: Objection.
9 Form.

10 THE WITNESS: I didn't read
11 every single article that he
12 referenced.

13 BY MR. VAUGHN:

14 Q. So you didn't come across
15 any of the literature that supported his
16 opinion -- or that would support his
17 opinion that only one dose of NDMA can
18 cause cancer?

19 A. No. And I did it -- I
20 commented on it in the context that
21 follows those two sentences.

22 And it's that, if the dose
23 is low enough, which was again, the focus
24 of my contentions, that a single dose

1 would be almost entirely metabolized by
2 the liver.

3 So I think it would be
4 better to put it into the context of what
5 I was referring to.

6 Q. Just to be clear, you did
7 not review all the literature that Dr.
8 Panigrahy did, correct?

9 A. Correct.

10 MR. VAUGHN: Can we go to
11 Page 26 of his expert report now.
12 BY MR. VAUGHN:

13 Q. Can you read that last
14 sentence that goes onto the next page.
15 It starts with, "A key step."

16 A. This is my report, right?

17 Q. Correct. This is your
18 report?

19 A. "A key step in this
20 metabolic activation to a potential
21 carcinogen is the hydroxylation of
22 NDMA/NDEA by cytochrome P450 pathways.
23 2E1 is almost exclusively for NDMA, and
24 both 2E1 and 2A6 are used for NDEA."

1 Q. And you have a citation
2 there, don't you?

3 A. Yes.

4 MR. VAUGHN: And can we
5 scroll down to see what that
6 citation is.

7 BY MR. VAUGHN:

8 Q. You found these authors of
9 this article to be credible, correct?

10 A. Correct.

11 Q. And experienced in the field
12 of nitrosamines?

13 A. I didn't look at each author
14 or even the first author's complete
15 publication list to see how many papers
16 they've written in that area. I've just
17 focused on what this one said.

18 Q. But the more papers they
19 wrote on it, probably the more
20 authoritative they are?

21 A. Potentially, yes.

22 MR. VAUGHN: Tyler, can we
23 go back now to Exhibit B, his
24 materials relied on. Let's go to

1 PDF Page 9. It's Page 8 on the
2 bottom of the document.

3 BY MR. VAUGHN:

4 Q. Doctor, if you look up about
5 five rows, you'll see this Kushida.
6 That's the article that you were citing
7 to a second ago in your expert report,
8 right?

9 A. Yes.

10 Q. Do you see the -- oh, I
11 think it's about the sixth, the
12 next-to-last name, T. -- I don't know
13 how you say that. Nohmi?

14 A. Mm-hmm. I see it.

15 Q. Do you recall if you
16 reviewed any other articles by this T.
17 Nohmi?

18 A. I don't think I did. I
19 don't recall that.

20 Q. Do you recall seeing other
21 papers by this T. Nohmi in Dr.
22 Panigrahy's expert report?

23 A. I may have seen that. But I
24 didn't read those.

1 Q. Okay. Well, let's have a
2 look at those.

3 MR. VAUGHN: Tyler, will you
4 pull up the Nohmi 2020 for us.

5 (Document marked for
6 identification as Exhibit
7 Bottorff-8.)

8 BY MR. VAUGHN:

9 Q. This first one that we were
10 looking at that you cited to is back in
11 2000. And this one now is in 2020. So
12 this -- Nohmi has at least been, you
13 know, involved in researching
14 nitrosamines for 20 years. Would you
15 agree with that?

16 A. I don't know what happened
17 in between. So there's a 20-year time
18 period between these two papers.

19 Q. He was studying nitrosamines
20 20 years ago, and he's still studying
21 nitrosamines though in 2020, right?

22 MS. THOMPSON: Object to
23 form.

24 THE WITNESS: That, I agree.

1 BY MR. VAUGHN:

2 Q. Right.

3 A. That, I agree. I just don't
4 know what happened in between.

5 Q. You don't know if he's
6 published additional papers in between
7 2000 and 2020, like in 2018, right?

8 A. Right. I did not look at
9 that.

10 MR. VAUGHN: Okay. Then if
11 we can go down about two-thirds of
12 the way under that first paragraph
13 under introduction. And there's a
14 sentence starting with "In
15 General."

16 BY MR. VAUGHN:

17 Q. Doctor, can you read that
18 sentence aloud for the jury?

19 A. "In general, genotoxic
20 carcinogens are regulated under the
21 policy that they have no thresholds or a
22 safe dose."

23 Q. And then how many citations
24 are listed after that?

1 A. Three.

2 Q. Do you know what ICH stands
3 for?

4 A. Yeah. I think it's a cancer
5 harmonization group or something like
6 that. International cancer harmonization
7 or something.

8 Q. And they are saying
9 genotoxic carcinogens are regulated under
10 the policy they have no threshold or safe
11 dose. You weren't aware of that when you
12 were forming your opinions, were you?

13 MS. THOMPSON: Objection.
14 Form.

15 THE WITNESS: I was aware
16 that there are people who think
17 from a regulatory standpoint that
18 way.

19 BY MR. VAUGHN:

20 Q. Why would regulators take
21 that stance?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: I'm not a

1 regulator. I don't know.

2 BY MR. VAUGHN:

3 Q. But you agree that a
4 genotoxin can alter a person's DNA,
5 correct?

6 MS. THOMPSON: Objection.
7 Form.

8 THE WITNESS: I agree that
9 that's the definition of a
10 genotoxin.

11 BY MR. VAUGHN:

12 Q. But you don't know if that
13 has any impact on if there should be a
14 safe threshold, do you?

15 A. Well, on that fact alone,
16 no, I don't think that's necessarily I
17 would agree with that.

18 Q. Go ahead and read the next
19 sentence for us.

20 A. "This is based on the
21 assumption that even one molecule of
22 genotoxic chemicals may induce a mutation
23 that may cause cancer."

24 Q. And then there's a couple

1 citations there as well, correct?

2 A. Correct.

3 Q. Did you happen to read
4 through of those citations either?

5 A. I did not. They were not
6 the focus in my report.

7 Q. I thought the focus of your
8 report was to see how little or how much
9 NDMA you can -- a human can -- scratch
10 that.

11 I thought the purpose of
12 your opinion was to figure out how much
13 NDMA a person can consume and not get
14 cancer, right?

15 MS. THOMPSON: Objection to
16 form.

17 THE WITNESS: Well, again,
18 there are words in here about
19 regulatory policy. I didn't
20 evaluate regulatory policy.

21 There are words in here
22 about assumption. I didn't
23 operate on assumptions.

24 I looked at the data. And

1 found that there were doses that
2 did not cause cancer.

3 BY MR. VAUGHN:

4 Q. And you're not trying to
5 give any regulatory opinions in this
6 litigation, correct?

7 A. Correct.

8 MS. THOMPSON: Objection to
9 form.

10 THE WITNESS: Sorry.

11 MS. THOMPSON: It's okay.

12 THE WITNESS: Correct.

13 BY MR. VAUGHN:

14 Q. The assumption is that one
15 molecule of a genotoxic chemical may
16 induce a mutation that may cause cancer.
17 This sentence though, what does that
18 actually have to do with regulatory?

19 MS. THOMPSON: Objection.
20 Form.

21 Where are you reading that
22 from?

23 THE WITNESS: The second
24 sentence.

1 BY MR. VAUGHN:

2 Q. Thank you, Doctor.

3 A. Again, the first sentence is
4 regulatory policy that I said I was not
5 going to give any opinions on.

6 The second sentence I said
7 made an assumption and then gave two
8 references.

9 And so for example,
10 Panigrahy's report references this
11 article. And this article only refers to
12 an assumption.

13 So what I don't know is if
14 this assumption is referring to papers
15 that also said assumption as opposed to
16 data proving it. So I can't really tell
17 you if this is just somebody repeating
18 assumption and assumption and assumption
19 and keep referring to it without having
20 any evidence or proof. They may have it.
21 I just can't tell from this.

22 Q. Because you haven't read
23 this and you haven't read any of the
24 citations, have you?

1 A. No. But now I have read
2 Panigrahy's reference or citation for
3 that, and there's no data here to support
4 that contention.

5 Q. I thought earlier -- I
6 thought your expert report you said you
7 did not have anything to support that
8 opinion?

9 MS. THOMPSON: Objection to
10 form.

11 THE WITNESS: I said he
12 didn't cite anything to form that
13 opinion.

14 BY MR. VAUGHN:

15 Q. So do you think this is the
16 only article that he based that opinion
17 on?

18 A. I do not know that. I know
19 that this article has no data with which
20 to make that conclusion that he made.

21 Q. But you haven't tried to
22 seek out any additional data regarding
23 genotoxic chemicals and their ability to
24 mutate someone's DNA and cause cancer

1 even with just one molecule, have you?

2 A. I haven't looked for that.

3 Although I have found animal data with
4 way more than one molecule being given
5 that did not produce cancer over the
6 entire lifetime of rats which corresponds
7 to anywhere between 70 and 90 years of
8 exposure in humans.

9 Q. And because you didn't look
10 for any literature on this, you cannot
11 base any of your opinions on the
12 literature that says this, right? You
13 didn't -- scratch that.

14 Because you didn't look for
15 any literature on genotoxic chemicals,
16 you also did not consider any of that
17 literature in forming your opinions in
18 this case; is that correct?

19 MS. THOMPSON: Objection.
20 Form.

21 THE WITNESS: These opinions
22 were not germane to the focus of
23 my report.

24 BY MR. VAUGHN:

1 Q. And explain to me again what
2 the focus of your report was?

3 MS. THOMPSON: Objection.
4 Asked and answered.

5 THE WITNESS: The metabolism
6 of NDMA and NDEA and in relation
7 to the amounts that were found in
8 valsartan, and in relation to
9 that, was there evidence based on
10 metabolism that there would be a
11 risk of cancer that I could
12 identify based on the animal data.

13 BY MR. VAUGHN:

14 Q. Doctor, can you tell the
15 jury how many molecules of NDMA are in
16 one nanogram?

17 MS. THOMPSON: Objection.
18 Form.

19 THE WITNESS: Let's see.
20 Can we do micrograms
21 instead?

22 BY MR. VAUGHN:

23 Q. Sure.

24 A. And the reason I say that is

1 this gets back to what are called molar
2 calculations, which use the molecular
3 weight of the compound in question, which
4 in the case of NDMA is -- the molecular
5 weight is 74. That's the weight of the
6 carbons an the oxygen and the nitrogens
7 and the hydrogens.

8 And they add up to 74. So a
9 microgram divided by 74 would be whatever
10 that ratio is in micromolar, and a mole
11 has Avoadra's number, 6.03 times ten to
12 the 23rd molecules.

13 So we can do that math if
14 you want.

15 Q. How about this? What's
16 larger, a nanogram or a molecule?

17 MS. THOMPSON: Objection.

18 THE WITNESS: A nanogram.

19 BY MR. VAUGHN:

20 Q. So there are multiple
21 molecules of NDMA in every nanogram of
22 NDMA?

23 A. Right. And so I'm doubting
24 that there's any way that you could prove

1 that one molecule could cause cancer
2 because there's no way to give one
3 molecule.

4 Q. You're saying they just
5 can't prove it, so you discount it?

6 A. And that's why this is an
7 assumption that I think is being passed
8 on from person to person.

9 And in your nursing career,
10 you may have heard of something called
11 chart lore where someone has heart
12 failure, because someone else in a note
13 said they had heart failure, and you
14 can't find any evidence of an ejection
15 fraction or heart failure meds or
16 anything to substantiate what we call
17 chart lore.

18 You can't give one molecule
19 of anything. We just don't do that.
20 There's no way to do it. So this is an
21 assumption that I think is being passed
22 on.

23 Q. An assumption based on the
24 fact that it's genotoxin and can alter

1 someone's DNA, right?

2 MS. THOMPSON: Objection.

3 THE WITNESS: At some dose.

4 But there's no way to prove it
5 happened at one molecule.

6 BY MR. VAUGHN:

7 Q. Would you say there's 100
8 molecules in a nanogram? A thousand?
9 How much do you think there approximately
10 would be?

11 A. It's based on the molecular
12 weight of the substance that you're
13 talking about.

14 Q. It would be more than 100?

15 A. Yeah, because we're talking
16 6.02 times ten to the 23rd for a
17 micromole. So that's a lot of molecules.

18 Q. Can you -- we'll go ahead
19 and do it in micrograms.

20 Can you give me an estimate
21 of how many of those molecules would be
22 in a microgram or a nanogram, either one?

23 A. Yeah. That's my estimate.

24 It's -- it's something like times ten to

1 the 20th or something like that.

2 Q. Per, is that microgram or
3 nanogram?

4 A. Per microgram.

5 Q. And what's ten to the 20th
6 for the jury?

7 A. Quadrillion billions or
8 something. I don't know what the exact
9 is.

10 Q. So per microgram, there's
11 you said quadrillion billions?

12 A. Oh, I don't know the exact
13 number. It's got 20 zeros in front of
14 the decimal point.

15 Q. 20 zeros. And then you are
16 aware of NDMA levels in valsartan that
17 are 40 micrograms. So you're saying
18 billions and billions and billions of
19 molecules of a genotoxic substance, you
20 don't think has the potential to cause
21 cancer, correct?

22 A. At the doses that we're --

23 MS. THOMPSON: Objection.

24 Form.

1 THE WITNESS: At the doses
2 that we're talking about that have
3 been demonstrated in the best
4 approximator we have, which is the
5 rat, that there is no cancer that
6 formed in billions times those
7 billions.

8 BY MR. VAUGHN:

9 Q. Just one nanogram, would
10 that be like trillions of molecules of
11 NDMA?

12 A. I'd have to do the math. I
13 couldn't assign a number to it unless I
14 did the math. But we're talking about a
15 lot.

16 Q. So these researchers have a
17 focus in carcinogens and NDMA. They
18 think one molecule of it can induce
19 cancer. And you, a pharmacist, thinks
20 that trillions of molecules of NDMA won't
21 even increase the risk of someone getting
22 cancer; is that correct?

23 MS. THOMPSON: Object to
24 form.

1 MS. KAPKE: Object to form.

2 THE WITNESS: What is
3 correct is that there have been no
4 data showing cancer in humans. So
5 we have to start there.

6 And just secondly, we have
7 millions and billions of molecules
8 being given to rats that don't
9 cause cancer.

10 And the NDMA in valsartan is
11 way less than that.

12 So that is what it is.

13 BY MR. VAUGHN:

14 Q. So the only evidence that's
15 going to be good enough for you is if we
16 give humans a bunch of NDMA and see what
17 happens? That's the only way that you're
18 going to say that it could be a
19 carcinogen in humans?

20 MS. THOMPSON: Objection to
21 form. Asked and answered.

22 THE WITNESS: It's not the
23 focus of my report.

24 The focus of my report is

1 whether the amount in valsartan
2 that we know, whether that
3 achieves some likelihood of
4 causing cancer based on the best
5 data we have, which are animal rat
6 data.

7 And so I concluded what I
8 did based on that.

9 BY MR. VAUGHN:

10 Q. Are you aware of the widely
11 understood principle that animal studies
12 may simply be underpowered to pick up the
13 cancer risk at very low levels?

14 MS. THOMPSON: Objection.
15 Form.

16 THE WITNESS: I am aware of
17 any study can be limited by the
18 lack of something showing up at
19 low doses. And that's what we
20 have. That's the data that we
21 have.

22 BY MR. VAUGHN:

23 Q. And are you aware that Peto
24 previously stated that too?

1 A. That Peto stated that we
2 have data showing that low doses won't
3 cause cancer?

4 Q. No, that Peto says that
5 animal studies were underpowered;
6 therefore, they wouldn't be able to
7 detect low doses increasing the risk of
8 cancer, which is why they extrapolate all
9 the way down to a no dose threshold.

10 Are you aware if Peto said
11 that?

12 MS. THOMPSON: Objection to
13 form.

14 THE WITNESS: I am aware of
15 Peto's study. I referenced it. I
16 referenced the concerns that he
17 also expressed about the accuracy
18 of the no threshold concept.

19 BY MR. VAUGHN:

20 Q. You said you are aware of
21 Peto study.

22 Is it your belief that Peto
23 has only done one study on NDMA?

24 A. I never said that. I was

1 referring to the one that I referred to
2 where he gave a low enough dose that we
3 could see there was no association with
4 cancers.

5 Q. Have you read all of Peto's
6 studies on NDMA?

7 A. I'd have to look at my
8 reference list. I think I've read at
9 least one or two others.

10 This was by far the largest.
11 So the reason he did a 4,000-rat study
12 was to address those concerns about not
13 having enough power to detect cancers at
14 low doses. So he improved his power by
15 doing what I thought was the largest rat
16 study, although it turns out that REMS
17 was almost the same size.

18 Q. I'm going to ask you one of
19 the questions again because I don't think
20 I got a clear answer.

21 One second. You said that
22 you're aware of the Peto study. And you
23 referenced it.

24 My question was, were you

1 aware that Peto said that he believed the
2 animal studies were underpowered and,
3 therefore, were not able to detect the
4 increased risk of cancer at low doses of
5 NDMA?

6 MS. THOMPSON: Objection.
7 Form.

8 THE WITNESS: And in that
9 paper, was it in his introduction
10 or in his conclusions?

11 BY MR. VAUGHN:

12 Q. You don't recall where it
13 was?

14 MS. THOMPSON: Objection.
15 Form.

16 THE WITNESS: I don't. We
17 could look it up. My suspicion is
18 that it's in his introduction to
19 explain why he chose to do a study
20 in 4,000 rats, is to address that
21 concern.

22 BY MR. VAUGHN:

23 Q. That's your suspicion, but
24 you don't know, do you?

1 A. No. We can call it up. We
2 can look at it. I would actually love to
3 do that.

4 Q. We might do that in front of
5 the jury instead.

6 MR. VAUGHN: Can we go back
7 to that Nohmi 2020 article,
8 please.

9 Can we zoom out a little
10 bit.

11 BY MR. VAUGHN:

12 Q. Can you read out loud,
13 Doctor, the next sentence starting with
14 "accordingly."

15 A. "Accordingly, genotoxic
16 carcinogens are strictly regulated and
17 not allowed to be used as food additives,
18 pesticides, or veterinary drugs."

19 Q. So genotoxic carcinogens
20 aren't even allowed in veterinary drugs
21 or pesticides, but it's your opinion that
22 it's okay for them to be in human
23 medications; is that correct?

24 MS. THOMPSON: Objection.

1 Form. Calls for speculation.

2 THE WITNESS: Again, at
3 doses low enough that don't appear
4 to increase the risk for cancer,
5 which is what I found, that is
6 reporting the science, not making
7 a regulatory statement, which is
8 not what I'm attempting to do.

9 BY MR. VAUGHN:

10 Q. Okay. Pesticides, it's not
11 like low amounts of NDMA are allowed in
12 pesticides. No NDMA is allowed to be in
13 a pesticide, right?

14 MS. THOMPSON: Objection.

15 Form. Scope.

16 THE WITNESS: I mean that's
17 what it says, yes.

18 BY MR. VAUGHN:

19 Q. And same for drugs that you
20 give to animals, it's not like you can
21 give a little bit. You can't give any at
22 all, right?

23 MS. THOMPSON: Objection.

24 Form. Scope.

1 THE WITNESS: Again --
2 sorry.

3 This is a regulatory
4 perspective. That's not the
5 approach I took.

6 BY MR. VAUGHN:

7 Q. Which one -- which approach
8 would be safer for the public health,
9 your approach or this approach?

10 MS. THOMPSON: Objection.
11 Form. Scope.

12 THE WITNESS: Again, you --
13 you are making the assumption that
14 one molecule causes cancer which
15 is an unsubstantiated claim.

16 So the reality is that we
17 have to look at what did happen,
18 not at what could or should or
19 might happen in the future.

20 But I was looking at the
21 reality of what did happen. And
22 did I feel that this put patients
23 at risk for developing cancer at
24 the amount in the valsartan

1 products.

2 And based on the best
3 available data that I have access
4 to, the answer is no, I don't
5 think it put people at excess
6 risk.

7 BY MR. VAUGHN:

8 Q. Again, you don't know all
9 the levels that were in valsartan,
10 because you never even asked defense
11 attorneys to provide it to you, did you?

12 MS. THOMPSON: Objection.
13 Form. Asked and answered.

14 THE WITNESS: I didn't ask
15 attorneys for that. I took it
16 from the FDA's website which was
17 publicly available to all of us.

18 BY MR. VAUGHN:

19 Q. Okay. I mean, I guess,
20 would you expect that a manufacturer of a
21 pharmaceutical product would disclose all
22 of their testing data to the FDA?

23 MS. THOMPSON: Objection.
24 Form.

1 THE WITNESS: They may have.
2 But the FDA didn't make it
3 available to me.

4 And even if we go back, I
5 think at the very beginning of
6 this morning, when you talked
7 about the 120 parts per billion,
8 let's call that the highest level.
9 It doesn't change the opinions in
10 my report anyway.

11 BY MR. VAUGHN:

12 Q. Did you just say parts per
13 billion? Did you mean parts per million?

14 A. If I said billion, I meant
15 million.

16 Sorry. The 120 parts per
17 million, which I think we calculated as
18 being just under 40 micrograms, like 38
19 something.

20 And so we're talking about,
21 instead of the calculations that I did on
22 20 micrograms, that 120 parts per
23 million, let's call it 40 micrograms.
24 And so instead of the amount in the

1 valsartan products that I calculated
2 being anywhere from 350 to 22,000 times,
3 you know, it's still 150 to 11,000 times.
4 So it doesn't change my opinions at all.

5 Q. The fact that you
6 underestimated the amount of NDMA in a
7 pill, the fact that you overestimated the
8 weight of the average human, the fact
9 that you did a one-to-one ratio when you
10 scaled it for kg, all of those things
11 together you don't think really impact
12 your opinion?

13 MS. THOMPSON: Objection to
14 form. Mischaracterizes his
15 testimony.

16 THE WITNESS: No. And just
17 making some assumptions that I
18 don't necessarily have to agree
19 with.

20 There's not a patient in
21 this country on valsartan for
22 hypertension at the usual age that
23 those people are that weigh
24 50 kilograms.

1 BY MR. VAUGHN:

2 Q. In the United States, right?

3 A. Is there one somewhere?

4 Yeah, probably.

5 Q. I mean, I guess Americans
6 are heavier on average than people in
7 other countries, aren't we?

8 A. Yeah, that's true.

9 Q. So --

10 A. Again, we're not talking
11 about healthy 17-years-olds. We're
12 talking about potentially unhealthy 50-,
13 60-, 70-year olds, who again aren't going
14 to be taking the drug for 70 years. At
15 most they could have been taking it for
16 four years.

17 Q. So if a company is making
18 valsartan and some of their product they
19 know has a lot of NDMA in it and some of
20 their product has just a little bit of
21 NDMA in it, do you think it would be more
22 appropriate for them to be sending that
23 high level of NDMA to Americans because,
24 you know, Americans weigh more than other

1 people do in other countries on average?

2 MS. THOMPSON: Objection.

3 Form. Foundation. Calls for
4 speculation.

5 THE WITNESS: I don't think
6 I ever said that. But I don't
7 think anyone would be doing that
8 anyway.

9 BY MR. VAUGHN:

10 Q. Why?

11 A. Why would they? I can't
12 come up with a reason why they would. So
13 I don't have a why.

14 Q. It would be very unethical
15 if they were doing that, wouldn't it?

16 MS. THOMPSON: Objection.
17 Form. Scope.

18 THE WITNESS: If someone
19 were to do something unethical, it
20 would be unethical.

21 BY MR. VAUGHN:

22 Q. I mean, if a company was
23 intentionally sending the higher level of
24 NDMA product to the United States instead

1 of other countries, that would be
2 unethical to do, right?

3 MS. THOMPSON: Objection.

4 Form. Asked and answered. Scope.
5 I mean, this is so far afield from
6 his opinions in his report, I
7 don't know what we're doing here.

8 BY MR. VAUGHN:

9 Q. You going to answer the
10 question, Doctor?

11 A. Yes, I can answer.

12 I can't understand how that
13 would ever happen. So I don't have an
14 opinion on something that would never
15 happen.

16 Q. I agree with you, it's
17 completely inconceivable someone would do
18 something like that.

19 Do you agree that a
20 responsible pharmaceutical company would
21 disclose all of their testing data and
22 all of the levels of NDMA that they were
23 aware of in valsartan to the FDA?

24 MS. THOMPSON: Objection to

1 form.

2 MS. KAPKE: Object to form.

3 MS. THOMPSON: I'm going to
4 re-raise the issue that was raised
5 earlier, that that is a general
6 liability opinion. That's not
7 about causation. That's not what
8 we're here to discuss.

9 MR. VAUGHN: Well, I mean,
10 the FDA has done some calculations
11 and stuff based on the data that
12 they're aware of. And this expert
13 has relied on what the FDA was
14 aware of.

15 So I think it is applicable.

16 BY MR. VAUGHN:

17 Q. You would expect a
18 responsible company to disclose all the
19 data that they are aware of to the FDA,
20 right?

21 MS. THOMPSON: Same
22 objection.

23 THE WITNESS: I'm assuming
24 they did. So I don't know what

1 happened there. It wasn't
2 anything that I looked at or
3 relied upon.

4 MR. VAUGHN: Great. Let's
5 take a break.

6 THE VIDEOGRAPHER: The time
7 right now is 3:55 p.m. We're off
8 the record.

9 (Short break.)

10 THE VIDEOGRAPHER: The time
11 right now is 4:06 p.m. We're back
12 on the record.

13 BY MR. VAUGHN:

14 Q. Doctor, can you hear me? It
15 says my connection is unstable. I think
16 it's good now.

17 A. I hear you now.

18 MS. THOMPSON: We hear you.

19 BY MR. VAUGHN:

20 Q. All right. Doctor, are you
21 aware -- strike that. Just going to talk
22 clearly.

23 Doctor, are you aware of how
24 the FDA selected the valsartan pills that

1 it tested for NDMA?

2 A. No, I'm not, actually. I
3 got the table that I included in my
4 report off of the FDA's published
5 website.

6 Q. And so you're not aware if
7 the companies sent the valsartan pills to
8 the FDA to test, correct?

9 A. I do not know that.

10 Q. And, therefore, you don't
11 know if those companies cherry-picked the
12 valsartan pills that they decided to send
13 to the FDA, correct?

14 A. I do not know that.

15 MR. VAUGHN: Thank you very
16 much for your time today, Doctor.
17 I have no further questions,
18 subject to direct.

19 THE WITNESS: Okay. All
20 right. Thank you, Mr. Vaughn.

21 MS. THOMPSON: We are going
22 to have some questions. And I
23 wasn't expecting you to do that.
24 So give me a second to pull those

1 up.

2 THE VIDEOGRAPHER: Are we
3 going off the record?

4 MR. VAUGHN: I'm fine with
5 staying on.

6 MS. THOMPSON: If you don't
7 mind, I'd really like to go off
8 for just two minutes just to make
9 sure that I have all my questions.

10 MR. VAUGHN: As long as it's
11 just a couple minutes.

12 MS. THOMPSON: Real brief.

13 THE VIDEOGRAPHER: The time
14 right now is 4:07 p.m. We're off
15 the record.

16 (Short break.)

17 THE VIDEOGRAPHER: The time
18 right now is 4:10 p.m. We're back
19 on the record.

20 MS. THOMPSON: Just a few
21 questions. Hopefully this will be
22 quick.

23 - - -

24 EXAMINATION

1 - - -

2 BY MS. THOMPSON:

3 Q. Dr. Bottorff, as a doctor of
4 pharmacy are you able to and have you
5 prescribed drugs to patients?

6 A. In the context of physically
7 writing the prescription, I have done
8 that.

9 Usually I've done it in an
10 environment where a physician at some
11 point would need to come behind and
12 co-sign it instead of independent
13 prescriptive authority, although there
14 are some pharmacists in some states who
15 have that ability. So yeah, I've
16 initiated, with co-signature, thousands
17 of drug therapies.

18 Q. And has that included
19 prescribing anti-hypertensives like
20 valsartan or other ARB drugs?

21 A. Valsartan, many of the other
22 ARBs, and not just for hypertension, but
23 also for heart failure.

24 Q. And you didn't study

1 valsartan and the other ARBs for their
2 metabolism or their pharmacokinetics for
3 the first time for this case, right?

4 A. No. No. Those are drugs
5 that on a regular basis, when they come
6 out, I look at their pharmacokinetics,
7 their pharmacodynamics, their side effect
8 profile. Because when you have more than
9 one drug in the category, then you need
10 to evaluate in what situation would I use
11 this one versus that one, what's the
12 strength of their outcome data, as much
13 clinical information on those drugs as I
14 can get.

15 And it's not just in my own
16 interest. I get asked questions about
17 those issues with these drugs from
18 physicians, from patients and from
19 students when I teach.

20 Q. We had some questions
21 earlier, and I just want to give you an
22 opportunity to explain it cleanly in a
23 way that a layperson -- and I am a
24 layperson -- can understand.

1 What is first-pass
2 metabolism?

3 A. Every drug that we give
4 orally that is absorbed towards the
5 liver, across the small intestine,
6 undergoes what we would call first-pass
7 metabolism.

8 And for some drugs that
9 clearance is pretty low, for some drugs
10 it's intermediate, and for some drugs
11 that clearance rate is really high.

12 And so the amount of drug
13 that gets through the liver, then into
14 the hepatic vein, which then enters the
15 circulation through the heart, the lungs,
16 back to the liver, to other organs, is
17 only occurring if drugs are given at a
18 dose that exceeds whatever that
19 first-pass metabolism capability is for
20 that particular drug.

21 Q. So did you have to determine
22 a first-pass metabolism capability for
23 valsartan and NDMA?

24 MR. VAUGHN: Object to form.

1 THE WITNESS: Sorry. For --
2 for valsartan, that's what's
3 reported in the package label and
4 plenty of studies showing --
5 that's when we talked about its
6 bioavailability being between,
7 what was it, 10 and 35 percent.

8 That's the percent of the
9 drug that gets through the liver
10 and does its systemic effects,
11 because that's a drug that you
12 want to work on the heart, in the
13 kidney, on the blood vessels.

14 Can you repeat the question
15 real quick?

16 BY MS. THOMPSON:

17 Q. I was asking about, did you
18 have to determine the first-pass
19 metabolism of both valsartan and then
20 NDMA --

21 A. Yeah, it's easier for
22 valsartan because it's supposed to get
23 through the liver and do its
24 pharmacologic effect so you can measure

1 the bloodstream to assess
2 bioavailability.

3 For NDMA, that assessment is
4 not as exact a science, except for a
5 couple small rat studies that looked at
6 it, because you don't want it to get into
7 the systemic circulation.

8 So -- and the dose is low
9 enough that you get first complete
10 first-pass metabolism, you couldn't
11 measure it in the bloodstream.

12 Q. And before valsartan that
13 contains NDMA or NDEA gets to the liver,
14 does it get metabolized anywhere else or
15 exposed to any organs prior to the liver?

16 A. No. And some drugs do.
17 There is a fairly robust round of
18 cytochrome P450 in the small intestine.
19 So many drugs are first metabolized
20 there, and then into the mesenteric blood
21 system directly into the liver.

22 But in looking at this
23 issue, particularly at 2E1, there is no
24 2E1 in the small intestine. So there is

1 no pre-systemic metabolism before it gets
2 to the liver. So all of it occurs in the
3 liver.

4 Q. And so, how do we know that
5 the only metabolism that would occur
6 would be in the liver and not prior to
7 that?

8 MR. VAUGHN: Object to form.

9 THE WITNESS: Because there
10 is no metabolism ability present
11 until you get to the liver.

12 BY MS. THOMPSON:

13 Q. Does first-pass metabolism
14 apply to both NDMA and NDEA?

15 A. Yes, it does.

16 Q. And you also used a term
17 earlier today that I'm going to again
18 make you explain to me like a layperson.

19 Liver saturation, can you
20 please explain that?

21 A. Again, this sort of gets at
22 the issue of first-pass metabolism and at
23 what point do you reach the ability of
24 the liver to completely clear the dose of

1 that drug.

2 And saturation is a good
3 term. Some people liken it to, like, how
4 much water can a sponge hold. And when
5 you've reached the point where the sponge
6 can hold no more water, the water gets
7 past the sponge to wherever it would go
8 after that.

9 So that's a way of thinking
10 of a saturation point. It's your ability
11 to measure it beyond the liver.

12 Q. Were you able to determine a
13 liver saturation level for NDMA or NDEA?

14 A. Not in the context of what
15 the actual dose would be based on blood
16 levels past the liver because it has such
17 a short half-life it's really difficult
18 to do.

19 So the surrogate for
20 measuring post-liver blood level
21 penetration, if you will, was whether
22 there was any either adducts or cancers
23 that occurred past that. So that's where
24 I came up with that

1 .1-milligram-per-kilogram sort of dose
2 that, if it does get through the liver,
3 it doesn't appear to cause any downstream
4 cancer. So it must be in small enough
5 amounts that it can't do that.

6 Q. Does NDMA or NDEA accumulate
7 in the liver if it is ingested every day?

8 A. That's a good question. In
9 a pharmacokinetic sense, drug metabolism
10 sense, for a drug to accumulate --
11 remembering that the liver's job is to
12 metabolize. And if you can't measure any
13 downstream, it's because the drug has
14 been completely metabolized in the liver,
15 so no drug level accumulation would occur
16 as long as you weren't exceeding that
17 capacity on a daily basis.

18 So in the doses that we are
19 talking about, there would be no drug
20 level accumulation.

21 Q. If valsartan makes it
22 through the liver and circulates into the
23 bloodstream and provides therapeutic
24 effect, how can you say that NDMA or NDEA

1 in it doesn't make it to that point?

2 A. We touched briefly on this.
3 I don't know how well I explained it.
4 But when a tablet of valsartan is
5 dissolved in the stomach and the upper
6 small intestine and then is absorbed, the
7 way I like to explain it, is that they
8 then go their merry way.

9 They are no longer
10 chemically connected. They have their
11 own separate and independent routes of
12 metabolism and elimination. And so
13 valsartan does what it does, and NDMA and
14 NDEA does what it does.

15 Q. And --

16 A. And those mechanisms do not
17 overlap at all.

18 Q. Is evaluating whether,
19 where, and how a drug is metabolized part
20 and parcel of pharmacokinetics?

21 A. Absolutely. I give examples
22 in my report of drugs whose doses are
23 dramatically different, or in some cases
24 aren't even given at all because

1 first-pass metabolism is so efficient
2 that the drug would be ineffective.

3 And a real classic example
4 of that is lidocaine. We don't use it
5 that much anymore for arrhythmias. But
6 when it was attempted to be given orally,
7 first-pass metabolism was so extensive
8 you've got no clinical effect from
9 lidocaine. Only if you gave it
10 intravenously.

11 So measurable kinetics,
12 clearance, half-life, first-pass
13 metabolism, that's all dependent on the
14 route of administration.

15 Q. And in your -- I hesitate to
16 put a number on there -- almost 40-year
17 career, have you done this type of
18 evaluation of whether, how, and where
19 drugs are metabolized in the body in your
20 ordinary course of your professional
21 experience?

22 MR. VAUGHN: Object to form.

23 THE WITNESS: I'm sorry.

24 Hundreds of times. There were how

1 many drugs in the cardiovascular
2 arena on the market when I
3 graduated compared to how many are
4 in the arena now in that 40 years,
5 how many more.

6 It's like hundreds and
7 hundreds more, and I do that for
8 every one of these drugs.

9 BY MS. THOMPSON:

10 Q. So the analysis that you've
11 done here to formulate your opinions, is
12 it consistent with what you've done in
13 your professional practice?

14 A. It is a process for any drug
15 that I go through. What's its dose, how
16 effective, what are its side effects,
17 what's its toxicity, what are the data,
18 what are the type of data. In many cases
19 I look at the animal studies in addition
20 to the human studies when they are
21 conducted.

22 Q. And you were asked earlier
23 about your kind of ultimate opinion that
24 the presence of NDMA in valsartan, based

1 on all of these factors, does not
2 increase the risk of cancer in downstream
3 organs. Do you recall that?

4 A. Yes.

5 Q. Okay. How do you know that?

6 MR. VAUGHN: Object to form.

7 THE WITNESS: It's my best
8 clinical judgment based on an
9 evaluation of the trials that have
10 a dose that did not cause cancer
11 in the most close animal model for
12 NDMA metabolism, which is the rat.
13 I identified a dose that below
14 which would not cause tumors.

15 And then in the multiple
16 tables that I provided, I compared
17 that to the milligram-per-kilogram
18 dose in the valsartan products
19 versus extrapolating to humans.
20 And it was hundreds and hundreds,
21 and even thousands and in some
22 cases tens of thousands of times
23 more.

24 So if we add that evidence,

1 which is the best we'll have,
2 we're not going to have any
3 better.

4 If that's the evidence that
5 we have of a dose and it doesn't
6 cause cancer --

7 (Brief interruption.)

8 BY MS. THOMPSON:

9 Q. Sorry, Doctor. If you want
10 to kind of go back and --

11 A. Poor child.

12 So again, using the animal
13 data, which is the best we have to
14 extrapolate into humans, a noncancerous
15 dose of NDMA which was about
16 .1 milligrams per kilogram -- and that
17 was fairly consistent across three or
18 four studies, at least that I looked at.
19 And you expressed that in a human dose
20 based on body weight, which is the best
21 way that we have to do it.

22 Then you get
23 valsartan-containing products, even if
24 you accept the 120 parts per million that

1 we talked about, there are still hundreds
2 to tens of thousands times more than what
3 doesn't cause cancer in a rat.

4 Q. I have one more question, at
5 least for now. We'll see if we have
6 anything further based on what you just
7 said. I hate to end on this note.

8 In preparing for this, did
9 you find a citation in your report that
10 you need to correct?

11 A. Thank you for bringing that
12 up.

13 When I went through some of
14 the epidemiology studies and constructed
15 my tables showing what I thought -- well,
16 what is the inconsistency in the data on
17 the association between NDMA proposed in
18 dietary and/or environmental exposures,
19 there were two studies by an author named
20 Straif.

21 And in my tables I reference
22 Straif and his data. But the citation I
23 quote is his other study and not the one
24 that actually has the data that I have in

1 there. So I just need to switch the
2 citation to the article that has those
3 data.

4 The data are accurate,
5 they're what I wanted to have in the
6 report, but his reference is the other
7 one that I read of his, not the one that
8 has these data.

9 MS. THOMPSON: And we'll
10 provide an updated version with
11 the correct citation for the other
12 Straif article. I don't know if
13 anybody else has anything else
14 that they wanted to cover.

15 MR. VAUGHN: I'll be quick
16 then.

17 - - -

18 EXAMINATION

19 - - -

20 BY MR. VAUGHN:

21 Q. Doctor, when did you realize
22 that your report had citation errors?

23 A. Yesterday afternoon. It has
24 a citation error.

1 Q. And how did that come to
2 your attention?

3 A. In just going through the
4 report and looking at some of where the
5 data came from. I think it actually it
6 was one of counsel that picked it up.

7 Q. Did you meet with counsel
8 prior to this deposition?

9 A. Yes.

10 Q. For how many hours?

11 A. Maybe six hours yesterday.

12 Q. Was yesterday the only day?

13 A. It's the only day that we
14 met in person.

15 Q. How many days did you meet
16 not in person or did you -- sorry not
17 meet. Strike that.

18 Did you also consult or prep
19 with attorneys by remote meetings?

20 A. There was a remote meeting
21 on Monday that just lasted a couple
22 hours.

23 Q. Are those the only two
24 meetings that you had in preparation for

1 your deposition?

2 A. Yes.

3 Q. I believe, just a few
4 minutes ago, you testified that NDMA is
5 not exposed to any organs prior to the
6 liver. Is that what you meant to say?

7 A. That is not what I said.

8 Q. Okay. So if the transcript
9 says that -- sorry.

10 A. Yeah, let me clarify.

11 It's not exposed to an organ
12 with metabolic capability prior to
13 getting to the liver.

14 Q. In your opinion, correct?

15 A. Yes, in my opinion.

16 Q. But there are several organs
17 that it touches prior to getting to the
18 liver?

19 A. Not in a metabolizing
20 capacity.

21 Q. But you would agree that it
22 at least touches several organs prior to
23 getting to the liver, correct?

24 A. It passes through the

1 esophagus in a solid pill form, which is
2 not where absorption would occur.

3 And then its dissolution to
4 be able to be absorbed occurs in the
5 stomach where there is no 2E1. And then
6 it's absorbed across the small intestine,
7 which also does not have 2E1. So the
8 first time it's in a form that can be
9 metabolized by 2E1 is when it gets to the
10 liver.

11 Q. When a substance is absorbed
12 through the small intestine, does
13 100 percent of it go to the liver or does
14 some of that blood bypass the liver?

15 MS. THOMPSON: Objection to
16 form.

17 THE WITNESS: Yeah, the
18 mesenteric system drains it all
19 into the liver. It's the
20 evolution of that defense
21 mechanism. That's what it's there
22 for.

23 BY MR. VAUGHN:

24 Q. The evolution, what do you

1 mean evolution of that defense mechanism?

2 A. Our evolution of the liver
3 doing what it does and the cytochrome
4 P450 system and other metabolizing
5 pathways that are not, you know, at hand
6 here, those evolved as a way of
7 detoxifying things that we ingested.

8 So the evolution of our
9 alimentary system and our drug
10 metabolizing system is the way it is to
11 be a detoxifying system.

12 Q. So is it your opinion that
13 because humans have been exposed to
14 environmental nitrosamines throughout
15 history, that humans have evolved to be
16 able to not get cancer from NDMA?

17 MS. THOMPSON: Objection.

18 Form.

19 THE WITNESS: Yeah, it's a
20 good line of thinking, but many of
21 these P450s evolved in response to
22 exposures that may have been other
23 toxins of other types that had
24 nothing to do with NDMA.

1 But because they're there
2 and now we are exposed to NDMA, we
3 have the capacity to metabolize.

4 BY MR. VAUGHN:

5 Q. So --

6 A. Some of these enzymes are
7 not so super specific that they evolve
8 only to handle one potential toxin.

9 Q. And is P450 one of those
10 that handles numerous toxins?

11 A. Yeah. There are like 250,
12 300 individually specific cytochrome P450
13 isozymes.

14 Q. Why haven't humans evolved
15 to just not be able to get cancer at all?

16 MS. THOMPSON: Objection.
17 Scope.

18 THE WITNESS: That is beyond
19 my ability to understand and
20 answer.

21 BY MR. VAUGHN:

22 Q. But you're able to give an
23 opinion that we've evolved to be able to
24 handle NDMA?

1 MS. THOMPSON: Objection.
2 Form. Mischaracterizes.

3 THE WITNESS: We have
4 evolved with the ability to
5 detoxify orally ingested
6 substances.

7 And I should add, it's a
8 little more complicated than I'm
9 portraying.

10 Many of the cytochrome P450s
11 are involved in endogenous
12 steroid, hormone, and cholesterol
13 metabolism. So some of them have
14 multiple jobs.

15 BY MR. VAUGHN:

16 Q. Do you have an opinion on
17 what animal a human evolved from?

18 MS. THOMPSON: Object to
19 form.

20 THE WITNESS: The -- I mean,
21 I'm pretty sure we evolved from
22 primates, from nonhuman primates.

23 BY MR. VAUGHN:

24 Q. But you think we metabolize

1 NDMA more like a rat than a nonhuman
2 primate?

3 MS. THOMPSON: Objection.
4 Asked and answered.

5 THE WITNESS: I think that
6 because that's what scientists
7 have said.

8 BY MR. VAUGHN:

9 Q. Does that really make sense,
10 if we evolved from a nonhuman primate,
11 that we're going to metabolize it more
12 like a rat?

13 MS. THOMPSON: Objection.
14 Asked and answered.

15 THE WITNESS: You know, why,
16 I don't know that I have an answer
17 for. It is just what it is. And
18 so I observed it, reported on it.

19 BY MR. VAUGHN:

20 Q. You noted lidocaine earlier.
21 Is Lidocaine a genotoxic carcinogen?

22 MS. THOMPSON: Objection.
23 Form.

24 THE WITNESS: I don't think

1 so. It's just an example of a
2 drug that has a very high
3 first-pass metabolism, and so
4 giving it orally will never
5 produce any post-liver effect. So
6 it's a good example in that
7 regard.

8 BY MR. VAUGHN:

9 Q. But the only genotoxic
10 carcinogen that you have experience with
11 is Actos, correct?

12 MS. THOMPSON: Objection.
13 Form. Mischaracterizes testimony.

14 THE WITNESS: No. I also
15 mentioned the immunosuppressive
16 drugs for heart transplant
17 patients. But that's pretty much
18 the extent.

19 BY MR. VAUGHN:

20 Q. Those are genotoxins?

21 MS. THOMPSON: Objection.
22 Form.

23 THE WITNESS: I'm not sure
24 their mechanism of cancer

1 production is genotoxic. But they
2 are carcinogenic.

3 BY MR. VAUGHN:

4 Q. Okay. So the only genotoxic
5 carcinogen that you have experience with
6 is Actos?

7 MS. THOMPSON: Objection.
8 Form.

9 THE WITNESS: In -- in that
10 specific genotoxic sense, yes.

11 BY MR. VAUGHN:

12 Q. Doctor, is every carcinogen
13 also a genotoxin?

14 MS. THOMPSON: Objection.
15 Form.

16 THE WITNESS: I don't think
17 so. But -- yeah, I don't think
18 so.

19 BY MR. VAUGHN:

20 Q. Were you an expert in the
21 Actos litigation at all?

22 A. No. That was just out of my
23 interest in -- when that report came out
24 about the potential association with

1 bladder cancer in the normal part of what
2 I do, is I look at the data and where it
3 came from, and how solid it is, and what
4 type of data. And Actos was one of those
5 drugs that a lot of my heart patients
6 were on.

7 Q. And so you wanted to
8 investigate it because you cared about,
9 you know, if your patients got cancer or
10 not, right?

11 MS. THOMPSON: Objection.
12 Form.

13 THE WITNESS: I investigated
14 it to evaluate the quality of the
15 data to make a determination in
16 that regard.

17 BY MR. VAUGHN:

18 Q. And in your opinion does
19 Actos actually incite bladder cancer or
20 increase the risk of bladder cancer?

21 MS. THOMPSON: Objection.
22 Form. Scope.

23 THE WITNESS: Certainly not
24 anything that I put into my

1 report. But my understanding is
2 that there was some inconsistency
3 in that data, so I don't think it
4 was very clear.

5 BY MR. VAUGHN:

6 Q. Did you keep all of your
7 patients on Actos?

8 MS. THOMPSON: Objection.
9 Form.

10 THE WITNESS: To the best of
11 my knowledge, yes.

12 BY MR. VAUGHN:

13 Q. Do you know if any of them
14 got bladder cancer?

15 MS. THOMPSON: Objection.
16 Form. Scope.

17 THE WITNESS: To the best of
18 my knowledge, no.

19 BY MR. VAUGHN:

20 Q. Are you aware of studies
21 that have shown that gastric and
22 colorectal tissues are more efficient at
23 metabolizing NDMA in humans than in
24 animals?

1 MS. THOMPSON: Objection.

2 Form.

3 THE WITNESS: I have not
4 seen that data. It didn't come up
5 in my research.

6 BY MR. VAUGHN:

7 Q. Is it easier to measure the
8 bioavailability of valsartan in
9 comparison to NDMA?

10 A. It's easier in the concept
11 that we can do that in humans and that
12 we've not done that with NDMA in humans.

13 Q. Didn't you say earlier it's
14 not well studied in humans?

15 MS. THOMPSON: Objection.

16 BY MR. VAUGHN:

17 Q. Or it's not studied at all,
18 I guess, is what you're saying?

19 A. Yeah, there are no
20 pharmacokinetic studies on NDMA in
21 humans. Maybe the one that was in
22 ranitidine that we mentioned earlier
23 today.

24 Q. So would you agree you don't

1 know actually how much NDMA gets into the
2 bloodstream?

3 MS. THOMPSON: Objection.
4 Form.

5 THE WITNESS: Because we
6 don't measure -- number one, we
7 don't know in humans. And because
8 we don't measure it in the animal
9 studies, I use the surrogates,
10 whether that was a development of
11 tumor or adducts.

12 BY MR. VAUGHN:

13 Q. But you agree that you do
14 not know how much would make it into the
15 bloodstream in a human, correct?

16 MS. THOMPSON: Objection.
17 Form. Asked and answered.

18 THE WITNESS: It depends on
19 the dose.

20 BY MR. VAUGHN:

21 Q. At the doses that we are
22 discussing -- that your expert report
23 covers, do you know how much NDMA gets
24 into the bloodstream of a human?

1 MS. THOMPSON: Objection.

2 Form. Asked and answered.

3 THE WITNESS: In a
4 quantitative amount in the rat
5 studies, no.

6 But not enough at the
7 .1-milligram-per-kilogram dose or
8 below to induce downstream cancer.

9 BY MR. VAUGHN:

10 Q. My question is more simple
11 than that. Just strictly in humans, you
12 do not know how much NDMA would get into
13 their bloodstream after they consumed
14 valsartan contaminated with NDMA,
15 correct?

16 MS. THOMPSON: Objection.

17 Form. Asked and answered.

18 THE WITNESS: We do not have
19 those data in humans. And so
20 we're relying on the best
21 surrogate we have, which is the
22 animal models, particularly the
23 rat.

24 BY MR. VAUGHN:

1 Q. And so you would agree that
2 you do not know how much NDMA would get
3 into the human bloodstream, correct?

4 MS. THOMPSON: Objection.
5 Form. Asked and answered.

6 THE WITNESS: Correct. We
7 do not have those human data.

8 BY MR. VAUGHN:

9 Q. And because you don't have
10 the data, you can't know, correct?

11 MS. THOMPSON: Objection.
12 Form. Asked and answered.

13 THE WITNESS: I do not know.

14 MR. VAUGHN: I have no
15 further questions.

16 MS. THOMPSON: One second.
17 I think we're done. Sorry.

18 MR. VAUGHN: Not a problem,
19 Sara.

20 MS. THOMPSON: Okay. Can we
21 go off.

22 MR. VAUGHN: Yeah.

23 THE VIDEOGRAPHER: The time
24 right now is 4:38 p.m. We're off

1 the record.

2 * * * * *

3 (Excused.

4 (Deposition concluded at
5 approximately 4:38 p.m. eastern
6 time.)

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1
2 CERTIFICATE
3
4

5 I HEREBY CERTIFY that the
6 witness was duly sworn by me and that the
7 deposition is a true record of the
8 testimony given by the witness.

9 It was requested before
10 completion of the deposition that the
11 witness, MICHAEL B. BOTTORFF, Pharm.D.,
12 have the opportunity to read and sign the
13 deposition transcript.

14
15 _____

16 MICHELLE L. GRAY,

17 A Registered Professional
18 Reporter, Certified Shorthand
19 Reporter, Certified Realtime
20 Reporter and Notary Public

21 Dated: September 20, 2021
22
23
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(The foregoing certification
of this transcript does not apply to any
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unless under the direct control and/or
supervision of the certifying reporter.)

1 INSTRUCTIONS TO WITNESS

2
3 Please read your deposition
4 over carefully and make any necessary
5 corrections. You should state the reason
6 in the appropriate space on the errata
7 sheet for any corrections that are made.

8 After doing so, please sign
9 the errata sheet and date it.

10 You are signing same subject
11 to the changes you have noted on the
12 errata sheet, which will be attached to
13 your deposition.

14 It is imperative that you
15 return the original errata sheet to the
16 deposing attorney within thirty (30) days
17 of receipt of the deposition transcript
18 by you. If you fail to do so, the
19 deposition transcript may be deemed to be
20 accurate and may be used in court.

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LIABILITY

ACKNOWLEDGMENT OF DEPONENT

I, _____, do
hereby certify that I have read the
foregoing pages, 1 - 391, and that the
same is a correct transcription of the
answers given by me to the questions
therein propounded, except for the
corrections or changes in form or
substance, if any, noted in the attached
Errata Sheet.

MICHAEL B. BOTTORFF, Pharm.D. DATE

Subscribed and sworn
to before me this
_____ day of _____, 20____.
My commission expires: _____

Notary Public

1	LAWYER ' S NOTES		
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